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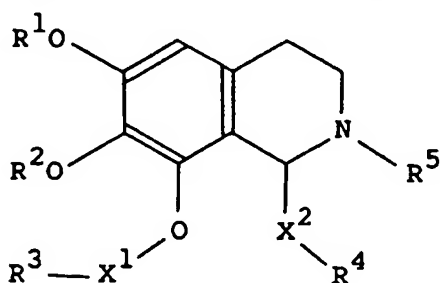
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(54) **Isoquinoline derivatives.**

(57) Novel isoquinoline derivatives represented by formula (I) :



(I)

wherein R¹, R², R³, R⁴, R⁵, X¹ and X² are as defined in the specification, have an anti-arrhythmic activity and bradycardiac activity and are effective for the treatment of arrhythmia, myocardiac infarction or angina pectoris.

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BACKGROUND OF THE INVENTION

Field of the Invention

5 The present invention relates to new isoquinoline derivatives having an anti-arrhythmic activity and bradycardiac activity and their medical use. The compounds of the present invention can be utilized as therapeutic agents in the medical field, especially, as agents for the treatment of arrhythmia, myocardiac infarction or angina pectoris.

10 Statement of the Related Art

As compounds having a selective bradycardiac activity, there are known alinidine, benzazepine derivatives (UL-FS49) [cf., *Drugs of the Future*, 10, 639 (1985)]. However, it has not been reported that isoquinoline derivatives analogous to the compounds of the present invention would have a bradycardiac activity and anti-arrhythmic activity.

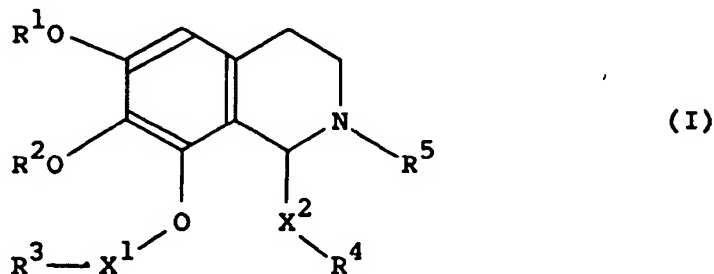
Currently, heart diseases have been a serious problem as clinical causes for death. It has thus been desired to develop an excellent agent for the treatment of heart diseases.

SUMMARY OF THE INVENTION

20 Accordingly, an object of the present invention is to provide a new isoquinoline derivative having an anti-arrhythmic activity and bradycardiac activity without adversely affecting blood pressure which is useful for the treatment of heart diseases, particularly, arrhythmia, myocardiac infarction or angina pectoris.

Another object of the present invention is to provide the medical use of the isoquinoline derivative.

25 According to the present invention, there are provided with a compound represented by general formula (I):



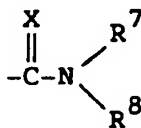
wherein each of R¹ and R² independently represents a lower alkyl group or both are combined together to form a methylene group;

X¹ represents a divalent alkylene chain having 1 to 5 carbon atoms which may be substituted with a lower alkyl group (one optional methylene group in which alkylene chain may be replaced by one group selected from the group consisting of an oxy group, a thio group, a sulfinyl group, a sulfonyl group or a group shown by formula: -NR⁶- wherein R⁶ represents a hydrogen atom or a lower alkyl group); provided that the said methyl-group is not the methylene group adjacent to the oxygen atom at the 8-position of the isoquinoline ring;

X² represents a divalent alkylene chain having 1 to 4 carbon atoms which may be substituted with a lower alkyl group;

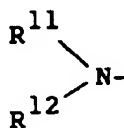
each of R³ and R⁴ represents independently an aryl group or a heteroaryl group, each of which groups may be substituted with 1 to 3 substituents, which may be the same or different and are selected from the group consisting of a lower alkyl group, a lower alkoxy group, a methylenedioxy group, a halogen atom, a nitro group, a hydroxy group, a cyano group, a lower alkoxycarbonyl group, a lower alkanoyl group, an amino group, an N-mono-lower alkylamino group, an N,N-di-lower alkylamino group, a carbamoyl group, an N-mono-lower alkyl-carbamoyl group, an N,N-di-lower alkylcarbamoyl group, an amino-lower alkyl group, an N-mono-lower alkyl-amino-lower alkyl group, an N,N-di-lower alkylamino-lower alkyl group, an N-(hydroxy-lower alkyl)amino-lower alkyl group, an N-lower-alkyl-N-(hydroxy-lower alkyl)amino-lower alkyl group, an N,N-di(hydroxy-lower alkyl)amino-lower alkyl group, an N-(lower alkoxy-lower alkyl)amino-lower alkyl group, an N-lower alkyl-N-(lower alkoxy-lower alkyl)amino-lower alkyl group, an N,N-di(lower alkoxy-lower alkyl)amino-lower alkyl group and a nitrogen-containing saturated heterocyclic lower alkyl group; and

R⁵ represents a lower alkoxy carbonyl group, a lower alkylsulfonyl group, a group shown by formula:



wherein each of R⁷ and R⁸ independently represents a hydrogen atom or a lower alkyl group which may be substituted with 1 or 2 substituents, which may be the same or different and are selected from the group consisting of a hydroxy group and a lower alkoxy group, or both are combined together with the nitrogen atom adjacent thereto to form a saturated nitrogen-containing heterocyclic group; and X represents an oxygen atom or a sulfur atom; or

a lower alkanoyl group which may be substituted with 1 or 2 substituents, which may be the same or different and are selected from the group consisting of a lower alkylsulfinyl group, a group shown by formula: R⁹S- wherein R⁹ represents a hydrogen atom, a lower alkyl group, a lower alkanoyl group, a carbamoyl group, an N-mono-lower alkylcarbamoyl group, an N,N-di-lower alkylcarbamoyl group or a lower alkoxy carbonyl group; a group shown by formula: R¹⁰O- wherein R¹⁰ represents a hydrogen atom, a lower alkyl group or a lower alkanoyl group which may be substituted with a hydroxy group; and a group shown by formula:



wherein each R¹¹ and R¹² independently represents a hydrogen atom, a lower alkyl group or a lower alkanoyl group, or both are combined together to form a 5- to 7-membered nitrogen-containing saturated heterocyclic ring having 3 to 6 carbon atoms together with the nitrogen atom adjacent thereto, wherein one methylene group not adjacent to the nitrogen atom for forming the ring may be replaced by an oxy group or a thio group and one methylene group adjacent to the nitrogen atom may be replaced by a carbonyl group, and a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Various terms referred to throughout the specification and embraced in the scope of the invention are defined below and specific examples are also given below.

The term "lower" is used to mean that the group or compound expressed by the term has carbon atoms of 6 or less, unless otherwise indicated. Therefore, the term "lower alkyl group" refers to a straight or branched alkyl group having 1 to 6 carbon atoms. Specific examples of the lower alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, 1-ethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-2-methylpropyl and 1-ethyl-1-methylpropyl.

Examples of the "lower alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy and isohexyloxy.

Examples of the "aryl group" include phenyl and naphthyl.

The term "heteroaryl group" is used to mean a monocyclic heteroaryl group containing hetero atom(s) such as an oxygen atom, a sulfur atom and a nitrogen atom. Examples of the heteroaryl group include pyridyl, furyl, thienyl, pyrrolyl and thiazolyl.

Examples of the "halogen atom" include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

Examples of the "lower alkoxy carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl and pentyloxycarbonyl.

Examples of the "lower alkanoyl group" include formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl and hexanoyl.

The term "N-mono-lower alkylamino group" is used to mean an amino group substituted with one lower alkyl group defined as described above and specific examples include N-methylamino, N-ethylamino, N-propylamino, N-isopropylamino and N-butylamino.

The term "N,N-di-lower alkylamino group" is used to mean an amino group substituted with two lower alkyl groups defined as described above which may be the same or different. Specific examples include N,N-dimethylamino, N-ethyl-N-methylamino, N,N-diethylamino, N-ethyl-N-propylamino, N,N-dipropylamino and N,N-di-butylamino.

The term "N-mono-lower alkylcarbamoyl group" is used to mean a carbamoyl group substituted with one lower alkyl group defined as described above. Specific examples include N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl and N-butylcarbamoyl.

The term "N,N-di-lower alkylcarbamoyl group" is used to mean a carbamoyl group substituted with two lower alkyl groups defined as above which may be the same or different. Specific examples include N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl and N-ethyl-N-propylcarbamoyl.

The term "amino-lower alkyl group" is used to mean a lower alkyl group defined above which is substituted with an amino group. Specific examples include aminomethyl, 1-aminoethyl, 2-aminoethyl, 1-aminopropyl, 2-aminopropyl, 3-aminopropyl, 1-amino-1-methylethyl, 2-amino-1-methylethyl, 1-aminobutyl, 2-aminobutyl, 3-aminobutyl and 4-aminobutyl.

The term "N-mono-lower alkylamino-lower alkyl group" is used to mean a lower alkyl group as defined above which is substituted with the N-mono-lower alkylamino group defined above. Specific examples include N-methylaminomethyl, 1-(N-methylamino)ethyl, 2-(N-methylamino)ethyl, 1-(N-methylamino)propyl, 2-(N-methylamino)propyl, 3-(N-methylamino)propyl, N-ethylaminomethyl, 1-(N-ethylamino)ethyl, 2-(N-ethyl-amino)ethyl, 1-(N-ethylamino)propyl, N-propylaminomethyl and N-isopropylaminomethyl.

The term "N,N-di-lower alkylamino-lower alkyl group" is used to mean a lower alkyl group as defined above which is substituted with the N,N-di-lower alkylamino group as described above. Specific examples include N,N-dimethylaminomethyl, 1-(N,N-dimethylamino)-ethyl, 2-(N,N-dimethylamino)ethyl, 1-(N,N-dimethyl-amino)propyl, 2-(N,N-dimethylamino)propyl, 3-(N,N-dimethylamino)propyl, N-ethyl-N-methylaminomethyl, 1-(N-ethyl-N-methylamino)ethyl, 2-(N-ethyl-N-methyl-amino)ethyl, N,N-diethylaminomethyl, 1-(N,N-diethyl-amino)ethyl, 2-(N,N-diethylamino)ethyl, N-ethyl-N-propylaminomethyl, N,N-dipropylaminomethyl and N,N-diisopropylaminomethyl.

The term "hydroxy-lower alkyl group" is used to mean a lower alkyl group defined as above which is substituted with one hydroxy group at the position other than 1-position thereof. Specific examples include 2-hydroxyethyl, 2-hydroxypropyl and 3-hydroxypropyl.

The term "N-(hydroxy-lower alkyl)amino-lower alkyl group" is used to mean a lower alkyl group as defined above which has an amino group substituted with one hydroxy-lower alkyl group as defined above. Specific examples include N-(2-hydroxyethyl)amino-methyl, 1-(N-(2-hydroxyethyl)amino)ethyl, 2-(N-(2-hydroxyethyl)amino)ethyl, N-(2-hydroxypropyl)aminomethyl and N-(3-hydroxypropyl)aminomethyl.

The term "N-lower alkyl-N-(hydroxy-lower alkyl)amino-lower alkyl group" is used to mean a lower alkyl group as defined above which contains an amino group substituted with the lower alkyl group defined as above and the hydroxy-lower alkyl group defined as above. Specific examples include N-(2-hydroxyethyl)-N-methylaminomethyl, 1-(N-(2-hydroxyethyl)-N-methyl-amino)ethyl, 2-(N-(2-hydroxyethyl)-N-methylamino)ethyl, and 3-(N-(2-hydroxyethyl)-N-methylamino)propyl.

The term "N,N-di(hydroxy-lower alkyl)amino-lower alkyl group" is used to mean a lower alkyl group as defined above which contains an amino group substituted with the two hydroxy-lower alkyl groups defined above which may be the same or different. Specific examples include N,N-di(2-hydroxy-ethyl)aminomethyl, 2-(N,N-di(2-hydroxyethyl)amino)ethyl, 3-(N,N-di(2-hydroxyethyl)amino)propyl and N-2-hydroxy-ethyl-N-3-hydroxypropylaminomethyl.

The term "lower alkoxy-lower alkyl group" is used to mean a lower alkyl group as defined above in which the hydrogen atom other than the 1-position is replaced by one lower alkoxy group as defined above. Specific examples include 2-methoxyethyl, 2-methoxypropyl and 3-methoxypropyl.

The term "N-(lower alkoxy-lower alkyl)amino-lower alkyl group" is used to mean a lower alkyl group as defined above which contains an amino group substituted with one lower alkoxy-lower alkyl group defined as described above. Specific examples include N-(2-methoxyethyl)aminomethyl, 1-(N-(2-methoxyethyl)-amino)ethyl, 2-(N-(2-methoxyethyl)amino)ethyl, N-(3-methoxypropyl)aminomethyl and N-(2-ethoxyethyl)-aminomethyl.

The term "N-lower alkyl-N-(lower alkoxy-lower alkyl)amino-lower alkyl group" is used to mean a lower alkyl group as defined above which contains an amino group substituted with the lower alkyl group defined above and the lower alkoxy-lower alkyl group defined above. Specific examples include N-(2-methoxyethyl)-N-

methylaminomethyl, 1-(N-(2-methoxyethyl)-N-methyl-amino)ethyl, 2-(N-(2-methoxyethyl)-N-methylamino)ethyl and N-ethyl-N-(2-methoxyethyl)aminomethyl.

The term "N,N-di(lower alkoxy-lower alkyl)-amino-lower alkyl group" is used to mean a lower alkyl group as defined above which contains an amino group substituted with two lower alkoxy-lower alkyl groups defined above which may be the same or different. Specific examples include N,N-di(2-methoxyethyl)-aminomethyl, 2-(N,N-di(2-methoxyethyl)aminoethyl, 3-(N,N-di(2-methoxyethyl)aminopropyl and N-(2-methoxyethyl)-N-(3-methoxypropyl)aminomethyl.

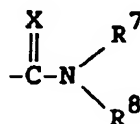
The term "nitrogen-containing saturated heterocyclic lower alkyl group" is used to mean a lower alkyl group as defined above which contains a 5- to 9-membered saturated heterocyclic ring having 3 to 8 carbon atoms which has at least one nitrogen atom in the ring thereof and the methylene group not adjacent to the nitrogen atom may be replaced by oxy, thio, sulfinyl or sulfonyl. Specific examples include pyrrolidinomethyl, pyrrolidin-2-ylmethyl, N-methylpyrrolidin-2-ylmethyl, 1-pyrrolidinoethyl, 2-pyrrolidinoethyl, 2-(pyrrolidin-2-yl)ethyl, 2-(N-methylpyrrolidin-2-yl)ethyl, 1,3-thiazolidin-3-ylmethyl, 1,3-thiazolidin-2-ylmethyl, N-methyl-1,3-thiazolidin-2-ylmethyl, 1-(1,3-thiazolidin-3-yl)ethyl, 2-(1,3-thiazolidin-3-yl)ethyl, 2-(N-methyl-1,3-thiazolidin-2-yl)ethyl, piperidinomethyl, piperidin-2-ylmethyl, N-methylpiperidin-2-ylmethyl, 1-piperidino-ethyl, 2-piperidinoethyl, 2-(piperidin-2-yl)ethyl, 2-(N-methylpiperidin-2-yl)ethyl, morpholinomethyl, morpholin-3-ylmethyl, N-methylmorpholin-3-ylmethyl, 1-morpholino-ethyl, 2-morpholinoethyl, 2-(morpholin-3-yl)ethyl, 2-(N-methylmorpholin-3-yl)ethyl, perhydro-1,4-thiazin-ylmethyl, perhydro-1,4-thiazin-3-ylmethyl, perhydro-N-methyl-1,4-thiazin-3-ylmethyl, 1-(perhydro-1,4-thiazin-4-yl)ethyl, 2-(perhydro-1,4-thiazin-4-yl)ethyl, 2-(perhydro-1,4-thiazin-3-yl)ethyl, 2-(perhydro-N-methyl-1,4-thiazin-3-yl)ethyl, perhydro-1,4-thiazin-1-oxid-4-ylmethyl, perhydro-1,4-thiazin-1-oxid-3-ylmethyl, perhydro-N-methyl-1,4-thiazin-1-oxid-3-ylmethyl, 1-(perhydro-1,4-thiazin-1-oxid-4-yl)ethyl, 2-(perhydro-1,4-thiazin-1-oxid-4-yl)ethyl, perhydro-1,4-thiazin-1,1-dioxid-4-ylmethyl, 2-(perhydro-1,4-thiazin-1,1-dioxid-4-yl)ethyl, piperazin-1-ylmethyl, 2-(piperazin-1-yl)ethyl, N-methylpiperazin-1-ylmethyl, 2-(N-methylpiperazin-1-yl)ethyl, N,N'-dimethylpiperazin-2-ylmethyl, 2-(N,N'-dimethylpiperazin-2-yl)ethyl, perhydroazepin-1-ylmethyl, 1-(perhydroazepin-1-yl)ethyl, perhydroazocin-1-ylmethyl and perhydroazonin-1-ylmethyl.

Examples of the "lower alkylsulfonyl group" include mesyl, ethylsulfonyl, propylsulfonyl, isopropyl-sulfonyl, butylsulfonyl, isobutylsulfonyl, sec-butyl-sulfonyl, tert-butylsulfonyl and pentylsulfonyl.

Examples of the "lower alkylsulfinyl group" include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl and butylsulfinyl.

Examples of the "lower alkylthio group" include methylthio, ethylthio, propylthio, isopropyl-thio, butylthio, isobutylthio and sec-butylthio.

Specific examples of the group shown by formula:

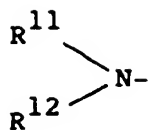


wherein each of R⁷ and R⁸ independently represents a hydrogen atom or a lower alkyl group which may be substituted with 1 or 2 substituents, which may be the same or different and are selected from the group consisting of a hydroxy group and a lower alkoxy group, or both R⁷ and R⁸ are combined together with the nitrogen atom adjacent thereto to form a saturated nitrogen-containing heterocyclic group; and X represents an oxygen atom or a sulfur atom,

include carbamoyl, N-methylcarbamoyl, N-ethyl-carbamoyl, N-(2-hydroxyethyl)carbamoyl, N-(2-methoxyethyl)carbamoyl, N-(2-hydroxypropyl)carbamoyl, N-(2-methoxypropyl)carbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-(2-hydroxyethyl)-N-methylcarbamoyl, N-(2-methoxyethyl)-N-methylcarbamoyl, N, N-diethylcarbamoyl, N,N-dipropylcarbamoyl, N-ethyl-N-(2-hydroxyethyl)carbamoyl, N-ethyl-N-(2-methoxyethyl)carbamoyl, N,N-di(2-hydroxyethyl)carbamoyl, N,N-di(2-methoxyethyl)carbamoyl, pyrrolidinocarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiocarbamoyl, N-methylthiocarbamoyl, N-ethylthiocarbamoyl, N-(2-hydroxyethyl)thiocarbamoyl, N-(2-methoxyethyl)-thiocarbamoyl, N-(2-methoxypropyl)thiocarbamoyl, N,N-dimethylthiocarbamoyl, N-ethyl-N-methylthio-carbamoyl, N-(2-hydroxyethyl)-N-methylthiocarbamoyl, N-(2-methoxyethyl)-N-methylthiocarbamoyl, N,N-diethylthiocarbamoyl and pyrrolidinothiocarbonyl.

Specific examples of the group shown by formula:

5



10 wherein each R^{11} and R^{12} independently represents a hydrogen atom, a lower alkyl group or a lower alkanoyl group, or both are combined together to form a 5- to 7-membered nitrogen-containing saturated heterocyclic ring having 3 to 6 carbon atoms together with the nitrogen atom adjacent thereto, wherein one methylene group not adjacent to the nitrogen atom for forming the ring may be replaced by an oxy group or a thio group and one methylene group adjacent to the nitrogen atom may be replaced by a carbonyl group,

15 include amino, N-methylamino, N,N-dimethylamino, N-ethyl-N-methylamino, N,N-diethylamino, N-acetylamin, N-acetyl-N-methylamino, N-propionylamino, N-methyl-N-propionylamino, 1,3-thiazolidin-3-yl, pyrrolidino, piperidino, morpholino, perhydro-1,4-thiazin-4-yl, perhydroazepin-1-yl, 2-pyrrolidon-1-yl and 2-piperidon-1-yl.

Examples of the "divalent alkylene chain having 1 to 5 carbon atoms which may be substituted with a lower alkyl group (one optional methylene group in which alkylene chain may be replaced by one group selected from the group consisting of an oxy group, a thio group, a sulfinyl group, a sulfonyl group or a group shown by formula: $-NR^6$ wherein R^6 represents a hydrogen atom or a lower alkyl group); provided that the said methylene group is not the methylene group adjacent to the oxygen atom at the 8-position of the isoquinoline ring" include

20 $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_2\text{CH}_3)-$, $-(\text{CH}_2)_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)-$, $-\text{OCH}_2-$, $-\text{SCH}_2-$, $-\text{N}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_3-$, $-\text{CH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)-$, $-\text{O}-(\text{CH}_2)_2-$, $-\text{S}-(\text{CH}_2)_2-$, $-\text{SO}-(\text{CH}_2)_2-$, $-\text{SO}_2$

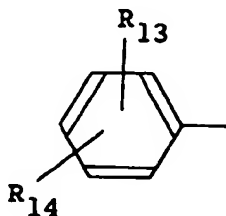
25 $-(\text{CH}_2)_2-$, $-\text{NH}-(\text{CH}_2)_2-$, $-\text{NCH}_3-(\text{CH}_2)_2-$, $-\text{OCH}(\text{CH}_3)\text{CH}_2-$, $-\text{SCH}(\text{CH}_3)\text{CH}_2-$, $-\text{SOCH}(\text{CH}_3)\text{CH}_2-$, $-\text{SO}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{NHCH}(\text{CH}_3)\text{CH}_2-$, $-\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_4-$, $-\text{CH}(\text{CH}_3)-(\text{CH}_2)_3-$, $-\text{CH}_2\text{CH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_3\text{CH}(\text{CH}_3)-$, $-\text{O}-(\text{CH}_2)_3-$, $-\text{S}-(\text{CH}_2)_3-$, $-\text{SO}-(\text{CH}_2)_3-$, $-\text{SO}_2-(\text{CH}_2)_3-$, $-\text{NH}-(\text{CH}_2)_3-$, $-\text{NCH}_3-(\text{CH}_2)_3-$, $-\text{CH}_2\text{O}-(\text{CH}_2)_2-$, $-\text{CH}_2\text{S}-(\text{CH}_2)_2-$, $-\text{CH}_2\text{SO}-(\text{CH}_2)_2-$, $-\text{CH}_2\text{SO}_2-(\text{CH}_2)_2-$, $-\text{CH}_2\text{NH}-(\text{CH}_2)_2-$, $-\text{CH}_2\text{N}(\text{CH}_3)-(\text{CH}_2)_2-$, $-(\text{CH}_2)_2\text{OCH}_2-$, $-(\text{CH}_2)_2\text{SCH}_2-$, $-(\text{CH}_2)_2\text{N}(\text{CH}_3)\text{CH}_2-$, $-\text{OCH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-\text{SCH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-(\text{CH}_2)_5-$, $-\text{CH}(\text{CH}_3)-(\text{CH}_2)_4-$, $-(\text{CH}_2)_4\text{CH}(\text{CH}_3)-$, $-\text{O}-(\text{CH}_2)_4-$, $-\text{S}-(\text{CH}_2)_4-$, $-\text{SO}-(\text{CH}_2)_4-$, $-\text{SO}_2-(\text{CH}_2)_4-$, $-\text{NH}-(\text{CH}_2)_4-$, $-\text{NCH}_3-(\text{CH}_2)_4-$, $-\text{CH}_2\text{O}-(\text{CH}_2)_3-$, $-\text{CH}_2\text{S}-(\text{CH}_2)_3-$, $-\text{CH}_2\text{SO}-(\text{CH}_2)_3-$, $-\text{CH}_2\text{SO}_2-(\text{CH}_2)_3-$, $-\text{CH}_2\text{NH}-(\text{CH}_2)_3-$, $-\text{CH}_2\text{N}(\text{CH}_3)-(\text{CH}_2)_3-$.

Examples of the "divalent alkylene chain having 1 to 4 carbon atoms which may be substituted with a lower alkyl group" include

35 $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_2\text{CH}_3)-$, $-(\text{CH}_2)_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)-$, $-(\text{CH}_2)_3-$, $-\text{CH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)-$, $-(\text{CH}_2)_4-$, $-\text{CH}(\text{CH}_3)-(\text{CH}_2)_3-$, $-\text{CH}_2\text{CH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-(\text{CH}_2)_2\text{CH}(\text{CH}_3)-(\text{CH}_2)_2-$, $-(\text{CH}_2)_3\text{CH}(\text{CH}_3)-$.

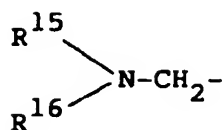
Preferred compounds of the present invention are the isoquinoline derivatives of formula (I), wherein each of R^1 and R^2 independently represents a lower alkyl group or both are combined together to form a methylene group; R^4 represents a phenyl group wherein 1 to 3 optional hydrogen atoms on the benzene ring may be replaced by 1 to 3 substituents selected from the group consisting of a lower alkoxy group and a methylenedioxy group, or a pyridyl group; X^2 represents CH_2 or CH_2CH_2 ; R^3 represents a group represented by formula:

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55 wherein R^{13} represents a hydrogen atom or a lower alkoxy group; and R^{14} represents an amino group, an N-mono-lower alkylamino group or an N,N-di-lower alkylamino group or represents a group shown by formula:

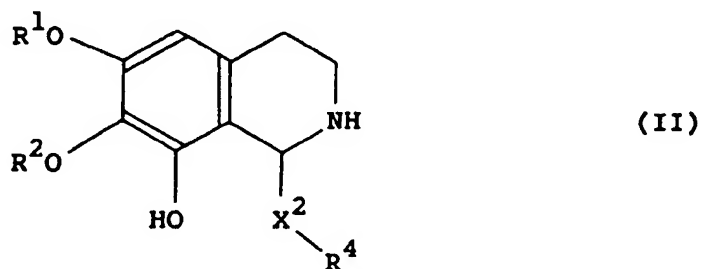


wherein each of R^{15} and R^{16} independently represents a hydrogen atom or a lower alkyl group wherein a hydrogen atom on the carbon atom not adjacent to the nitrogen atom may be replaced by a hydroxy group or a lower alkoxy group; or both R^{15} and R^{16} are combined together with the nitrogen atom adjacent thereto to form a 5- to 7-membered nitrogen-containing saturated heterocyclic ring having 3 to 6 carbon atoms and in this case, one optional methylene group not adjacent to the nitrogen atom may be replaced by one group selected from the group consisting of oxy, thio, sulfinyl, sulfonyl or a group shown by formula: $-\text{NR}^{17}-$ wherein R^{17} represents a hydrogen atom or a lower alkyl group, or

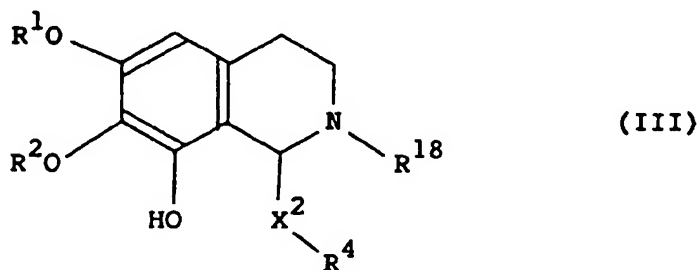
a pyridyl group wherein 1 or 2 hydrogen atoms on the pyridine ring may be replaced by 1 or 2 substituents selected from the group consisting of a lower alkoxy group and an N,N-di-lower alkylaminomethyl group.

Processes for preparing the compounds (I) of the present invention are explained below.

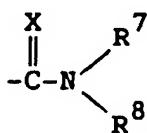
The compounds of the present invention represented by general formula (I) described above can be prepared by alkanoylation, alkoxycarbonylation, carbamoylation or sulfonylation of 1,2,3,4-tetrahydro-isoquinolin-8-ol derivatives (II) represented by general formula (II):



wherein R^1 , R^2 , X^2 and R^4 are as described above; and then condensing the resulting derivatives (III):



wherein R^1 , R^2 , X^2 and R^4 have the same significations as described above; and R^{18} represents a lower alkoxy-carbonyl group, a lower alkylsulfonyl group, a group represented by formula:



wherein R^7 and R^8 have the same significances as described above, or a lower alkanoyl group wherein the lower alkanoyl group may be substituted with 1 or 2 substituents selected from the group consisting of a lower alkylsulfinyl group, a lower alkylthio group, a hydroxy group, a lower alkoxy group and an N,N-di-lower alkylamino group,

on the hydroxy group at the 8-position of the isoquinoline ring, with compounds (IV) represented by general formula (IV):

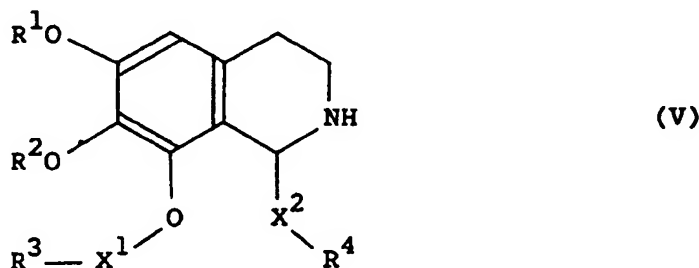


wherein R^3 and X^1 are as described above; and Y represents a splitting off group which is generally replaceable by an aryloxy group,

in the presence of a base (referred to as Process 1).

Alternatively, the compounds of the present invention can be prepared by performing substitution of one halogen atom in α,α' -dihaloxylenes (o-, m-, p-) with the compounds (III) in a manner similar to Process 1 and then substituting another halogen atom remained with primary or secondary amines (referred to as Process 2).

Furthermore, compounds obtained in Process 1 or Process 2 in which R^{18} is formyl can be converted into the desired compounds by subjecting the formyl compounds to alkali hydrolysis to remove the formyl, if necessary, then subjecting the resulting derivatives (V):



wherein R^1 , R^2 , R^3 , R^4 , X^1 and X^2 have the same significances as described above, to alkanoylation, alkoxycarbonylation, carbamoylation or sulfonylation at the 2-position of the isoquinoline ring, and further where a suitable splitting off group is present on the introduced substituent of the compounds obtained by the alkanoylation, substituting the splitting off group with nucleophilic agents such as thiol compounds, primary or secondary amines and amide compounds (referred to as Process 3). Where the compounds obtained by process 3 contain an acylthio group, the acylthio group may be converted into a mercapto group, if desired, by alkali hydrolysis (referred to as Process 4). Where the compounds obtained by processes 1 to 3 contain a nitro group in R^3 and/or R^4 , the nitro group may be converted into a primary amino group using an appropriate reducing agent (referred to as Process 5). Where the compounds obtained by Processes 1 to 3 contain a thio group, the thio group may be converted into a sulfinyl group or a sulfonyl group using an appropriate oxidizing agent, if necessary (Process 6).

Hereafter these processes are described more specifically.

Process 1

The alkanoylation of Compound (II) at the 2-position of the isoquinoline ring can be performed by reacting a carboxylic acid reactive derivative (for example, an acid halide, an acid anhydride, an activated amide, an activated ester) corresponding to the alkanoyl group to be introduced, with (II) in an appropriate solvent (for example, chloroform, dichloromethane, dimethylformamide, tetrahydrofuran, 1,4-dioxane) at 0°C to room temperature, if necessary, in the presence of an appropriate basic for example, triethylamine, pyridine, 4-N,N-dimethylaminopyridine). The alkoxycarbonylation and sulfonylation may be conducted in a similar manner by reacting (II) with an alkoxycarbonyl halide or a sulfonyl halide corresponding to the group to be introduced. The carbamoylation may be effected either by reacting (II) with a carbamoyl halide corresponding to the group to be introduced, in the same manner as in the alkanoylation, or by reacting isocyanate or isothiocyanate with (II) at 0°C to room temperature in an appropriate solvent (for example, chloroform, dichloromethane, tetrahydrofuran, 1,4-dioxane).

The condensation of Compound (III) with Compound (IV) is carried out preferably in an appropriate solvent. Examples of the solvent used are acetone, acetonitrile, methanol, 1,4-dioxane, tetrahydrofuran, dimethylsulfoxide and dimethylformamide. Examples of the base used in the reaction include inorganic bases such as alkali

metal carbonates, alkali metal hydrogencarbonate, alkali metal hydroxides, alkali metal hydrides and alkali metal alkoxides. In general, the reaction can be carried out by dissolving Compound (III) in the solvent described above, adding a suitable base to the solution, further adding Compound (IV) and then reacting the mixture at 0°C to 80°C.

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Process 2

The condensation of Compound (III) with α,α' -dihaloxylenes (o-, m-, p-) is carried out in the same manner as in Process 1. The substitution of one halogen atom remained on the group introduced in the resulting compound may be performed by adding an excess amount of a primary or secondary amine to be introduced in an appropriate solvent (for example, methanol, ethanol, 1,4-dioxane, dimethylformamide or dimethylsulfoxide) and reacting them at 0°C to the boiling point of the solvent.

Process 3

The synthesis of Compound (V) via deformylation by alkali hydrolysis can be performed by adding 1 equivalent to an excess amount of alkali metal hydroxide aqueous solution to the starting compound in an appropriate solvent (methanol, ethanol or 1,4-dioxane) and reacting them at room temperature to the boiling point of the solvent. The alkanoylation, alkoxy-carbonylation, carbamoylation and sulfonylation may be performed in a manner similar to Process 1. Where the alkanoyl group has a splitting off group, the introduction of the thiol compound by substitution of this splitting off group can be performed by reacting the thiol compound with the starting compound in a suitable solvent (for example, methanol, ethanol, chloroform, tetrahydrofuran, dimethylformamide or dimethyl sulfoxide) at 0°C to the boiling point of the solvent, if necessary, in the presence of an appropriate base (for example, an organic base such as triethylamine and pyridine; an inorganic base such as an alkali metal hydroxide, an alkali metal carbonate, an alkali metal hydrogencarbonate, an alkali metal hydride and an alkali metal alkoxide).

The introduction of the primary or secondary amine can be performed as in Process 2. The introduction of the amide compound may be carried out by reacting the amide compound with the starting compound in an appropriate solvent (tetrahydrofuran, dimethylformamide or 1,4-dioxane) at 0°C to the boiling point of the solvent in the presence of an appropriate base (for example, an alkali metal hydride).

Process 4

The conversion of the acylthio group into the mercapto group by alkali hydrolysis may be conducted by adding an aqueous solution of an appropriate base (for example, an alkali metal hydroxide, an alkali metal carbonate, an alkali metal hydrogencarbonate, ammonia) in an appropriate solvent (for example, methanol, ethanol, 1,4-dioxane) to the starting compound and then reacting them at 0°C to the boiling point of the solvent.

Process 5

The conversion of the nitro group to the primary amino group through reduction may be carried out by adding tin (II) chloride to the starting compound in an appropriate solvent (for example, ethanol or ethyl acetate) and reacting them at 60°C to the boiling point of the solvent.

Process 6

The conversion of the thio group into the sulfinyl group or sulfonyl group by oxidation may be carried out by adding an appropriate oxidizing agent (for example, oxone, m-chloroperbenzoic acid, hydrogen peroxide) to the starting compound in an appropriate solvent (for example, chloroform, dichloromethane, acetic acid or acetone) and reacting them at 0°C to 60°C. An amount of the oxidizing agent used is in the range of 1 to 1.2 equivalents in the case of sulfinylation and in the range of 2 to 3 equivalents in the case of sulfonylation, based on the starting compound having the thio group.

Compounds (I) obtained by these processes contain stereoisomers based on the presence of asymmetric carbon at the 1-position of the isoquinoline ring. Where the starting Compound (II) is a racemic mixture, the racemic mixture is subjected to optical resolution using an appropriate optically active acid in a conventional manner and the respective processes described above are applied to the products, whereby the respective stereoisomers may be synthesized. As the appropriate acid used for the optical resolution, there are (+)-tartaric acid, (-)-tartaric acid, (+)-dibenzoyltartaric acid and (-)-dibenzoyltartaric acid. The starting material, 1,2,3,4-tet-

rahydroisoquinoline derivatives [II] may be synthesized by the known method (see PCT/JP89/00825, WO90/02119). That is, Compound [II] may be prepared from phenethylamines via Bischler-Napieralski reaction.

5 The starting Compound (IV) may be synthesized by converting the hydroxy group of aminoalcohols obtained by known methods [for example, see Japanese Patent Application KOKAI (Laid-Open) No. 55-53247, J. Med. Chem., 27, 1047 (1984)] into a splitting off group in a conventional manner. That is, Compound (IV) may be synthesized either by reacting with a reagent such as thionyl chloride, thionyl bromide, phosphorus pentachloride, phosphorus oxychloride, etc. in the absence of any solvent or in an appropriate solvent (for example, chloroform or dichloromethane) thereby to convert into the halide or by reacting with a reagent such
10 as methanesulfonyl chloride and p-toluenesulfonyl chloride to convert into the mesylate or tosylate.

Preferred compounds of the present invention are listed in the following Table.

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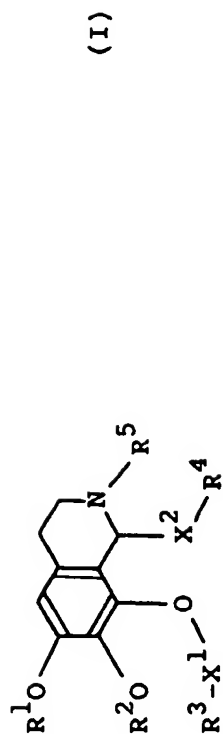
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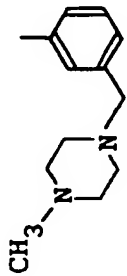
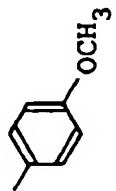
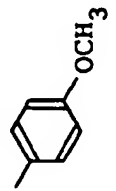
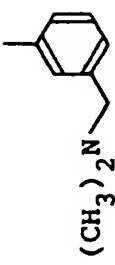
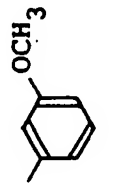
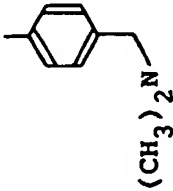
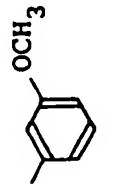
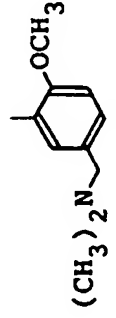
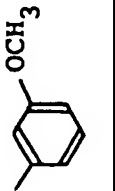
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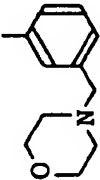
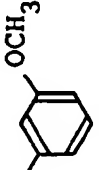

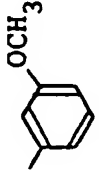

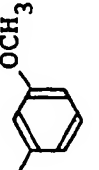
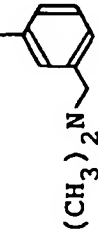
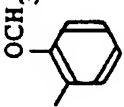
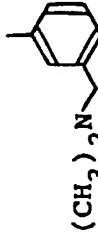
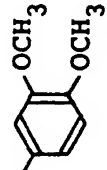
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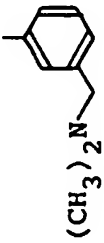
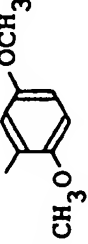
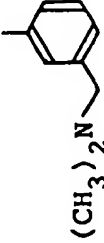
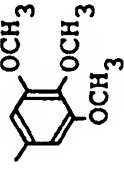
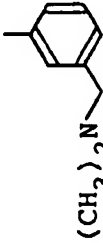

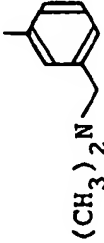
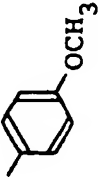

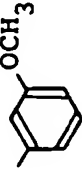
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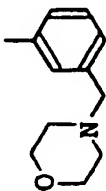
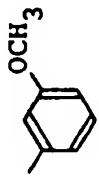

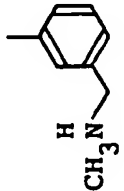
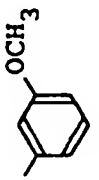
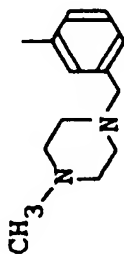
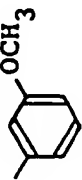
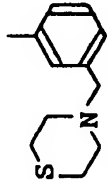
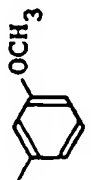


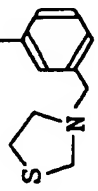
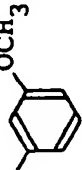
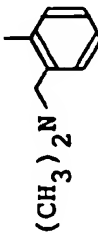
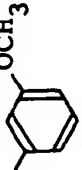
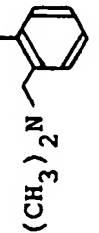
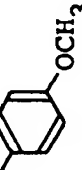
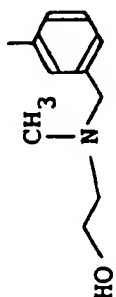
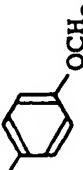
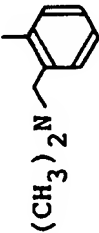
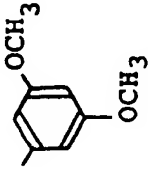
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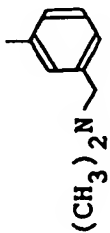
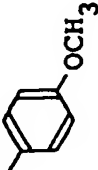
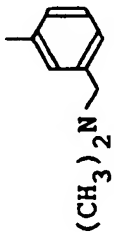
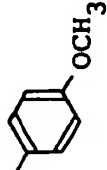
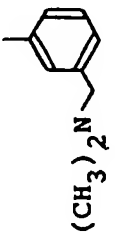
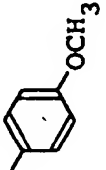
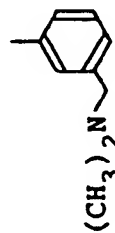
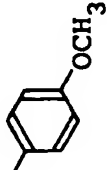
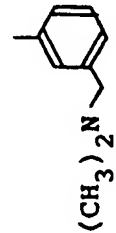
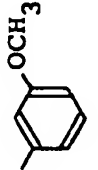
| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|----------------|---|--------------------|
| 5 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 6 | CH ₃ - | CH ₃ - | Ph- |  | -CHO | $\text{-CH}_2\text{-N(CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-)}\text{CH}_3$ | -CH ₂ - |
| 7 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 8 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
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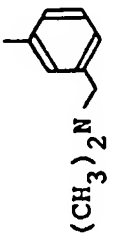
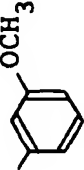
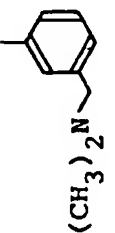
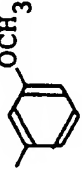
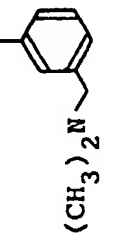
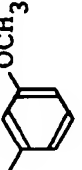
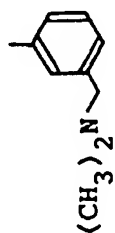
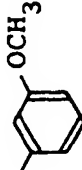
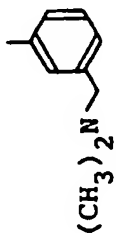
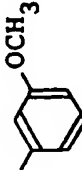
| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|---|----------------|--------------------|--------------------|
| 10 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 11 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 12 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 13 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
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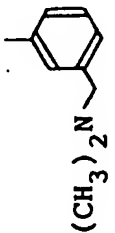
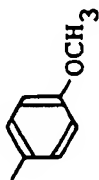
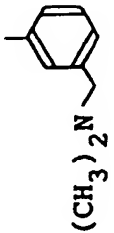
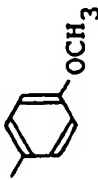
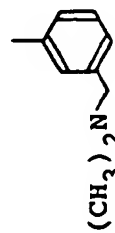
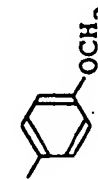
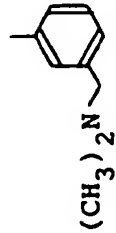
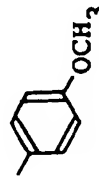
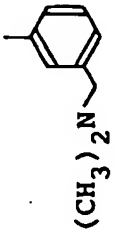
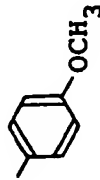
| Com- pound No. | R ¹ - | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|--------------------|--------------------|---|--|----------------|--------------------|------------------------------------|
| 15 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 16 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 17 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 18 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ CH ₂ - |
| 19 | -CH ₂ - | -CH ₂ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |

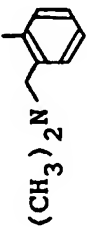
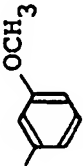
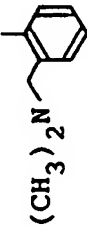
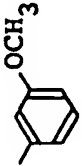
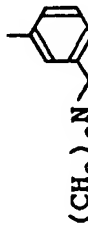
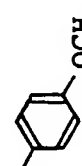

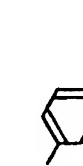


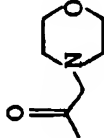
| Compound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|--------------|--------------------|-------------------|---|--|----------------|-------------------------------------|--------------------|
| 20 | -CH ₂ - | |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 21 | CH ₃ - | CH ₃ - | Ph- |  | -CHO | -S(CH ₂) ₄ - | -CH ₂ - |
| 22 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 23 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 24 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |

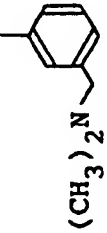
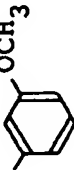
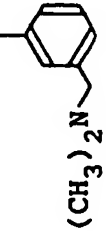
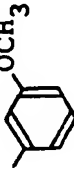
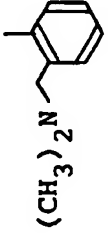
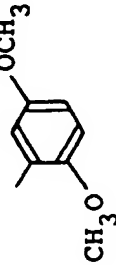
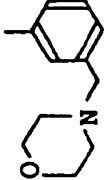
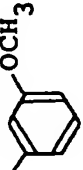
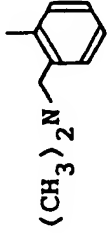
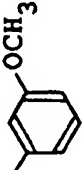
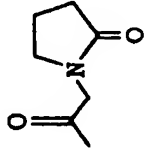
| Com- pound No . | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|-----------------------|-------------------|-------------------|---|--|----------------|--------------------|--------------------|
| 25 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 26 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 27 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 28 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 29 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |

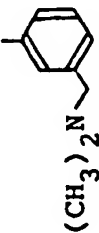
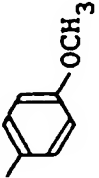
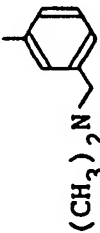
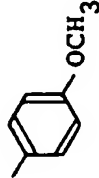
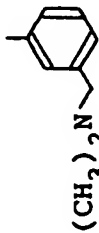
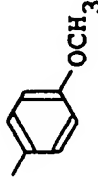
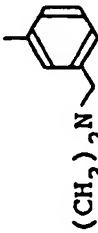
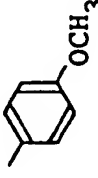
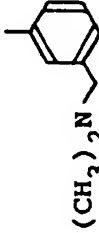
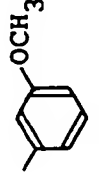
| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|---------------------------------------|--------------------|--------------------|
| 30 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ OH | -CH ₂ - | -CH ₂ - |
| 31 | CH ₃ - | CH ₃ - |  |  | -CO(CH ₂) ₂ OH | -CH ₂ - | -CH ₂ - |
| 32 | CH ₃ - | CH ₃ - |  |  | -COCH(OH)CH ₃ | -CH ₂ - | -CH ₂ - |
| 33 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ OCH ₃ | -CH ₂ - | -CH ₂ - |
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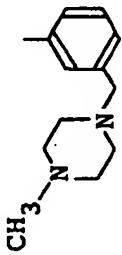
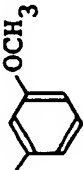

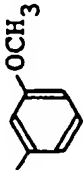

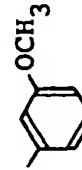

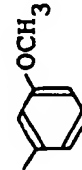
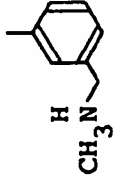
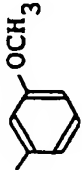
| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|---|--------------------|--------------------|
| 35 | CH ₃ - | CH ₃ - |  |  | -CO(CH ₂) ₂ OH | -CH ₂ - | -CH ₂ - |
| 36 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ OCH ₃ | -CH ₂ - | -CH ₂ - |
| 37 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ N(CH ₃)COCH ₃ | -CH ₂ - | -CH ₂ - |
| 38 | CH ₃ - | CH ₃ - |  |  | -SO ₂ CH ₃ | -CH ₂ - | -CH ₂ - |
| 39 | CH ₃ - | CH ₃ - |  |  | -COCH ₃ | -CH ₂ - | -CH ₂ - |

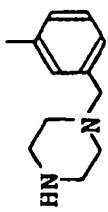
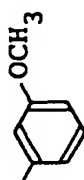
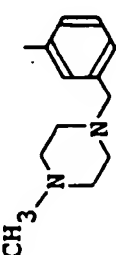
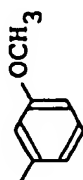
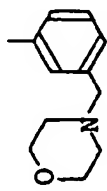
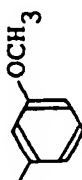
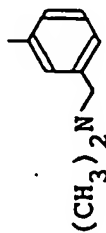
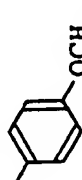
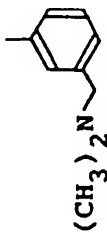
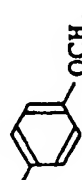
| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|---|--------------------|--------------------|
| 40 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |
| 41 | CH ₃ - | CH ₃ - |  |  | -CSNHCH ₃ | -CH ₂ - | -CH ₂ - |
| 42 | CH ₃ - | CH ₃ - |  |  | -CONH(CH ₂) ₂ OH | -CH ₂ - | -CH ₂ - |
| 43 | CH ₃ - | CH ₃ - |  |  | -CON(CH ₃) ₂ | -CH ₂ - | -CH ₂ - |
| 44 | CH ₃ - | CH ₃ - |  |  | -CONH ₂ | -CH ₂ - | -CH ₂ - |

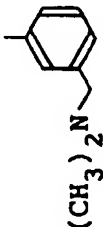
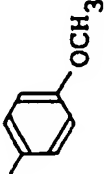
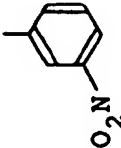
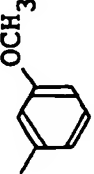
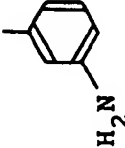
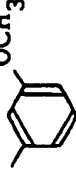
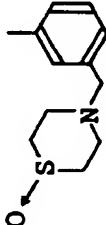
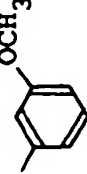
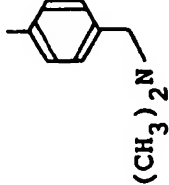
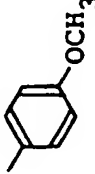
| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|---|--------------------|--------------------|
| 45 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |
| 46 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ OH | -CH ₂ - | -CH ₂ - |
| 47 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ SCOCH ₃ | -CH ₂ - | -CH ₂ - |
| 48 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ SCH ₃ | -CH ₂ - | -CH ₂ - |
| 49 | CH ₃ - | CH ₃ - |  |  |  | -CH ₂ - | -CH ₂ - |

| Compound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|--------------|--------------------|--------------------|---|--|---|--------------------|--------------------|
| 50 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ SCH ₃ | -CH ₂ - | -CH ₂ - |
| 51 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ SCOCH ₃ | -CH ₂ - | -CH ₂ - |
| 52 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ SCOCH ₃ | -CH ₂ - | -CH ₂ - |
| 53 | -CH ₂ - | -CH ₂ - |  |  | -COCH ₂ SCOCH ₃ | -CH ₂ - | -CH ₂ - |
| 54 | CH ₃ - | CH ₃ - |  |  |  | -CH ₂ - | -CH ₂ - |

| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|---|--------------------|--------------------|
| 55 | CH ₃ - | CH ₃ - |  |  | -CO ₂ CH ₃ | -CH ₂ - | -CH ₂ - |
| 56 | CH ₃ - | CH ₃ - |  |  | -SO ₂ CH ₃ | -CH ₂ - | -CH ₂ - |
| 57 | CH ₃ - | CH ₃ - |  |  | -COCH ₃ | -CH ₂ - | -CH ₂ - |
| 58 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ N(CH ₃) ₂ | -CH ₂ - | -CH ₂ - |
| 59 | CH ₃ - | CH ₃ - |  |  | -CO ₂ CH ₃ | -CH ₂ - | -CH ₂ - |

| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|----------------------------------|--------------------|--------------------|
| 60 | CH ₃ - | CH ₃ - |  |  | -CO ₂ CH ₃ | -CH ₂ - | -CH ₂ - |
| 61 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |
| 62 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |
| 63 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |
| 64 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |

| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|--|--------------------|--------------------|
| 65 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |
| 66 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |
| 67 | CH ₃ - | CH ₃ - |  |  | -CONHCH ₃ | -CH ₂ - | -CH ₂ - |
| 68 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ OCOCH ₃ | -CH ₂ - | -CH ₂ - |
| 69 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ OCOCH ₂ OH | -CH ₂ - | -CH ₂ - |

| Com- pound No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | X ¹ | X ² |
|----------------------|-------------------|-------------------|---|--|-----------------------|--------------------|--------------------|
| 70 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ SH | -CH ₂ - | -CH ₂ - |
| 71 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 72 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 73 | CH ₃ - | CH ₃ - |  |  | -CHO | -CH ₂ - | -CH ₂ - |
| 75 | CH ₃ - | CH ₃ - |  |  | -COCH ₂ OH | -CH ₂ - | -CH ₂ - |

The pharmacological activities of the compounds according to the present invention are described below.

Effect on ventricular fibrillation and mortality induced by coronary artery occlusion and reperfusion in rats:

Under anesthesia with pentobarbital, male Sprague Dawley (SD) rats were thoracotomized. The compounds of the present invention were studied with respect to the influence on ventricular fibrillation and mortality induced by reperfusion after ligation of the left coronary artery for 5 minutes. At the same time, blood pressure and heart rate were determined through a catheter inserted into the carotid artery. Each test compound was intravenously administered 2 minutes prior to the ligation. The results are shown in Table 1. The hydrochloride of Compound 1 was intraduodenally administered 30 minutes before the ligation. The results are shown in Table 2.

Table 1. Effect on ventricular fibrillation and mortality induced
by reperfusion after coronary artery ligation in rats
(intravenous administration)

| Test Compound | Dose (mg/kg) | Number of animals | Incident rate of ventricular fibrillation (%) | Mortality rate (%) | Change in blood pressure (%) | Change in heart rate (%) |
|------------------|-----------------|-------------------------|--|--------------------------|---------------------------------------|-----------------------------------|
| Control | | 5 | 100 | 100 | 6.3 | -6.8 |
| Cpd. 1 | 1 | 5 | 20 | 0 | 1.8 | -15.0 |
| Cpd. 15 | 1 | 5 | 20 | 0 | 1.9 | -9.9 |
| Cpd. 17 | 1 | 5 | 0 | 0 | 10.0 | -12.5 |
| Cpd. 18 | 1 | 5 | 60 | 20 | 3.7 | -13.3 |
| Cpd. 33 | 1 | 5 | 40 | 20 | 7.2 | -11.4 |
| Cpd. 40 | 1 | 5 | 40 | 0 | -0.5 | -11.5 |
| Cpd. 43 | 1 | 5 | 20 | 0 | 6.8 | -11.6 |
| Cpd. 46 | 1 | 5 | 20 | 20 | -5.2 | -21.3 |
| Cpd. 49 | 1 | 5 | 0 | 0 | 1.0 | -9.3 |

- cont'd -

Table 1 (cont'd)

| | | | | | | |
|----------------|---|---|-----|-----|------|-------|
| Cpd. <u>50</u> | 1 | 5 | 60 | 40 | 5.2 | -13.8 |
| Cpd. <u>52</u> | 1 | 5 | 20 | 0 | -8.8 | -15.6 |
| Cpd. <u>55</u> | 1 | 5 | 40 | 20 | 6.4 | -11.5 |
| Cpd. <u>58</u> | 1 | 5 | 0 | 0 | -4.0 | -7.9 |
| Cpd. <u>59</u> | 1 | 5 | 0 | 0 | 1.3 | -16.5 |
| Cpd. <u>67</u> | 1 | 5 | 40 | 40 | 2.6 | -11.7 |
| Cpd. <u>70</u> | 1 | 5 | 20 | 20 | -8.5 | -18.1 |
| Lidocaine | 1 | 5 | 100 | 100 | -4.7 | -12.3 |

As shown in Table 1, the compounds of the present invention prevent the occurrence of ventricular fibrillation and mortality rate in the dose of 1.0 mg/kg and the effects were more potent than those with Lidocaine. In this case, a remarkable bradycardiac activity was noted. As demonstrated above, the compounds of the present invention are effective for the conditions induced by reperfusion after coronary artery ligation.

Table 2. Effect on ventricular fibrillation and mortality induced by reperfusion after coronary artery ligation in rats (intraduodenal administration)

| Test Compound | Dose (mg/kg) | Number of animals | Incident rate of ventricular fibrillation (%) | Mortality rate (%) |
|----------------------|--------------|-------------------|---|--------------------|
| Control | | 6 | 100 | 50 |
| Cpd. 1 hydrochloride | 10 | 6 | 33.3 | 0 |
| | 50 | 6 | 0 | 0 |

As shown in Table 2, Compound 1 hydrochloride at doses of 10 and 50 mg/kg dose-dependently prevented ventricular fibrillation and mortality rate induced by coronary artery occlusion and reperfusion after intraduodenal administration in rats. This result indicates that intraduodenal administration of the compound of the present invention is effective for the conditions induced by reperfusion after coronary artery ligation.

Effect on ventricular fibrillation induced in dog by reperfusion after coronary artery ligation in dogs:

Under anesthesia with pentobarbital, both sexes beagle dogs were thoracotomized. The compounds of the present invention were studied with respect to the influence on ventricular fibrillation and mortality induced by reperfusion after ligation of the left coronary artery for 30 minutes. Test compound (Compound 1 hydrochloride) and Verapamil were intravenously administered 5 minutes prior to the ligation. The results are shown in Table 3.

**Table 3. Effect on ventricular fibrillation in dog
induced by reperfusion after coronary artery
ligation in dogs**

| Test Compound | Dose (mg/kg) | Number of animals | Incident rate of ventricular fibrillation (%) |
|-------------------------|-----------------|-------------------------|--|
| Control | | 10 | 90 |
| Cpd. 1 Hydrochloride | 1.0 | 10 | 30 |
| Verapamil | 0.1 | 10 | 50 |

As shown in Table 1, Compound 1 hydrochloride markedly inhibited ventricular fibrillation in the dose of 1.0 mg/kg. The effect was more potent than that of Verapamil at the dose of 0.1 mg/kg. As demonstrated above, the compound of the present invention is also effective for the conditions induced in dog by reperfusion after coronary artery ligation in dogs.

The foregoing results of the pharmacological studies reveal that the compounds of the present invention exhibit the anti-arrhythmic activity and bradycardiac activity. Therefore, the present invention can provide an effective method for the treatment of arrhythmia, myocardial infarction and angina pectoris.

As mode for application of the anti-arrhythmic and bradycardiac agents according to the present invention, various forms can be selected depending upon purposes. There are, for example, oral preparations such as tablets, capsules, powders, granules, liquid or elixir, etc. and parenteral preparations such as sterilized liquid forms, e.g., liquid or suspension, etc.

Solid preparations may be prepared in the form of tablets, capsules, granules or powders as they are but appropriate additives may also be used for the preparations. Examples of such additives include sugars such as lactose, glucose, etc.; starch of corn, wheat, rice, etc.; fatty acids such as stearic acid, etc.; inorganic salts such as magnesium metasilicate aluminate, anhydrous calcium phosphate, etc.; synthetic high molecular substances such as polyvinylpyrrolidone, polyalkylene glycol, etc.; fatty acid salts such as calcium stearic acid, magnesium stearate, etc.; alcohols such as stearyl alcohol or benzyl alcohol, etc.; synthetic cellulose derivatives such as methyl cellulose, carboxy methylcellulose, ethyl cellulose, hydroxypropylmethyl cellulose, etc.; and other additives conventionally used, such as water, gelatin, talc, vegetable oils, gum arabic, etc.

In general, these capsule, tablet, granule and powder preparations contain the effective ingredient in an amount of 0.1 to 100 wt%, preferably 1 to 100 wt%.

The liquid preparation is prepared in the form of a suspension, syrup or injection, using appropriate additives generally used in liquid preparations, using water, alcohols or vegetable oils such as soybean oil, peanut oil or sesame oil, etc.

As suitable solvents in the case of parenteral administration such as intramuscular injection, intravenous injection or subcutaneous injection, there are, for example, distilled water for injection, Lidocaine hydrochloride solution (for intramuscular injection), physiological saline, glucose aqueous solution, ethanol, liquid for intravenous injection (for example, aqueous solution of citric acid and sodium citrate, etc.) or electrolyte solution (for drip injection and intravenous injection), etc. or a mixture thereof.

These injections may be previously dissolved or may also be in such a form that they are provided in the form of powders by adding appropriate additives thereto and are dissolved upon use. These injections contain the effective ingredient generally in the range of 0.005 to 10 wt%, preferably in the range of 0.05 to 5 wt%.

The liquid preparation for oral administration such as a suspension or syrup contains the effective ingredient in the range of 0.1 to 50 wt%.

The dose of the anti-arrhythmic, anti-myocardial infarction or anti-angina pectoris agent of the present invention may vary depending upon age, health state, body weight or conditions of the patient but its daily dose

is in the range of 0.01 to 1 mg/kg for parenteral administration and in the range of 0.1 to 10 mg/kg for oral administration, for adult.

Hereafter the present invention is described in more detail by referring to the examples but is not deemed to be limited thereto.

5

REFERENTIAL EXAMPLE 1

Preparation of 2-formyl-6,7-dimethoxy-1-(4-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 1)

10 To a suspension of 6,7-dimethoxy-1-(4-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (2.26 g, 6.86 mmole) in chloroform (60 ml) was added formic trimethylacetic anhydride (1.16 g, 8.91 mmole) at 0°C. The mixture was stirred for 30 minutes and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give intermediate 1 (2.23 g) as colorless crystals.

m.p.: 171-173°C

15 FAB-MS(m/z, (C₂₀H₂₃NO₅+H)⁺): 358

Intermediates 2~10 (Referential Examples 2~10) were prepared using the corresponding 1,2,3,4-tetrahydro-isoquinoline derivatives, according to the reaction in Referential Example 1.

REFERENTIAL EXAMPLE 2

20

2-Formyl-6,7-dimethoxy-1-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 2)

m.p.: 163-167°C

FAB-MS(m/z, (C₂₀H₂₃NO₅+H)⁺): 358

25

REFERENTIAL EXAMPLE 3

2-Formyl-6,7-dimethoxy-1-(2-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 3)

m.p.: 156-157°C

FAB-MS (m/z, (C₂₀H₂₃NO₅+H)⁺): 358

30

REFERENTIAL EXAMPLE 4

2-Formyl-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 4)

m.p.: 155-157 °c

35 FAB-MS (m/z, (C₂₁H₂₅NO₆+H)⁺): 388

REFERENTIAL EXAMPLE 5

2-Formyl-6,7-dimethoxy-1-(2,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 5)

40 m.p.: 143.0-144.5°C

FAB-MS (m/z, (C₂₁H₂₅NO₆+H)⁺): 388

REFERENTIAL EXAMPLE 6

45 2-Formyl-6,7-dimethoxy-1-(3,4,5-trimethoxybenzyl)-1,2,3, 4-tetrahydroisoquinolin-8-ol (intermediate 6)

m.p.: 190-195 °c

FAB-MS (m/z, (C₂₂H₂₇NO₇+H)⁺): 418

REFERENTIAL EXAMPLE 7

50

2-Formyl-6,7-dimethoxy-1-(3-pyridylmethyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 7)

m. p.: 199-200 °c

FAB-MS (m/z, (C₁₈H₂₀N₂O₄+H)⁺): 329

55

REFERENTIAL EXAMPLE 8

2-Formyl-6,7-dimethoxy-1-(4-methoxyphenethyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 8)

m.p.: 151.0-152.5°C

FAB-MS (m/z, (C₂₁H₂₅NO₆+H)⁺): 372

REFERENTIAL EXAMPLE 9

- 5 2-Formyl-1-(3-methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 9)
 m. p.: 205-207 °C
 FAB-MS (m/z, (C₁₉H₁₉NO₅+H)⁺): 342

REFERENTIAL EXAMPLE 10

- 10 2-Formyl-6,7-dimethoxy-1-(3,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (intermediate 10)
 m.p.: 176.5-178.0°C
 FAB-MS (m/z, (C₂₁H₂₅NO₆+H)⁺): 388

15 REFERENTIAL EXAMPLE 11

(1) Preparation of (-)-6,7-dimethoxy-1-(4-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol

- (-)-6,7-Dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (+)-dibenzoyl-D-tartrate was obtained from (±)-6,7-dimethoxy-1-(4-methoxybenzyl)-1, 2,3,4-tetrahydroisoquinolin-8-ol and (+)-dibenzoyl-D-tartaric acid by a conventional method. The salt was purified by repeated recrystallizations from chloroform-acetone-methanol (10:6:1).

m.p.: 173.0-174.0°C (dec)

Optical Rotation: [α]_D²⁵ = +58.3° (C=0.336, methanol)

- The salt was treated with a saturated aqueous sodium hydrogencarbonate solution to give the captioned compound as colorless crystals.

Optical Rotation: [α]_D²⁵ = -15.8° (C=0.419, chloroform)

(2) Preparation of (+)-6,7-dimethoxy-1-(4-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol

- 30 The combined mother liquors of recrystallization in the above (1) were concentrated and the residue was treated with a saturated aqueous sodium hydrogen-carbonate solution to give crude (+)-6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol. The compound was treated with (-)-dibenzoyl-L-tartaric acid to give (+)-6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (-)-dibenzoyl-L-tartrate. The salt was purified by repeated recrystallizations from chloroform-acetone-methanol (10:6:1).

35 m.p.: 172.0-173.0°C (dec)

Optical Rotation: [α]_D²⁵ = -65.6° (C=0.308, methanol)

The salt was treated with a saturated aqueous sodium hydrogencarbonate solution to give the captioned compound as colorless crystals.

Optical Rotation: [α]_D²⁵ = +16.6° (C=0.445, chloroform)

40 EXAMPLE 1

(1) Preparation of Compound 1

- 45 Intermediate 1 obtained in Referential Example 1 (360 mg, 1.01 mmole) was dissolved in dimethyl sulfoxide (6ml), and potassium hydroxide (245 mg, 3.71 mmole, 85%) was added, and the reaction mixture was stirred under nitrogen at room temperature for 5 minutes. To the mixture was added dropwise a solution of 3-chloro-methyl-N,N-dimethylbenzylamine hydrochloride (267 mg, 1.21 mmole) in dimethyl sulfoxide (6ml) over a period of 1 hour, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate and washed successively with water and brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by MPLC (Merck, Lichroprep Si 60/chloroform:methanol=40:1~10:1) to give the captioned compound (420mg) as a colorless oil.

IR(neat, cm⁻¹): 2944, 1677, 1611, 1515, 1431, 1344, 1248, 1179, 1122, 1086, 1032, 753

FAB-MS(m/z, (C₃₀H₃₆N₂O₅+H)⁺): 505

- 55 ¹H-NMR(300MHz, CDCl₃, δ ppm):

2.21+2.27(6H,s × 2), 2.65(1H,dd,J=10.7Hz, 13.7Hz), 2.70-2.91(2H,m), 3.07(1H,dd,J=2.5Hz, 13.7Hz), 3.10-3.29+4.41(2H,m+ddd,J=2.1Hz, 6.7Hz, 13.2Hz), 3.39+3.44+3.48-3.52(2H,d × 2+m,J=13.5Hz, J=13.5Hz), 3.74+3.75(3H,s × 2), 3.86+3.88(3H,s × 2), 3.93(3H,s), 4.30+5.73(1H,dd × 2,J=2.5Hz, 10.7Hz, J=3.4Hz, 9.0Hz), 5.11(1H,d,

J=10.9Hz), 5.28+5.35(1H, d, $J=10.9$ Hz, $J=10.9$ Hz), 6.39+6.46(1H, s \times 2), 6.64-6.87(4H, m), 7.19(1H, s), 7.30-7.39+7.46-7.52(3H, m \times 2), 7.41+7.97(1H, s \times 2)

(2) Preparation of Compound 1 hydrochloride

Compound 1 was dissolved in methanol containing hydrogen chloride. The mixture was concentrated under reduced pressure, and the residue was recrystallized from a mixture of methanol and diethyl ether to give the captioned compound as a colorless powder.

m.p.: 161-167°C

High Resolution FAB-MS (m/z, $(C_{30}H_{38}N_2O_5+H)^+$):

Calcd.: 505.2702

Found : 505.2719

Compounds 2~6 (Examples 2~6) were prepared by the reaction of intermediate 1 (Referential Example 1) with the corresponding chlorides, N-(3-chloromethyl-benzyl)pyrrolidine hydrochloride, N-(3-chloromethyl-benzyl)morpholine hydrochloride, 4-chloromethyl-N,N-di-methylbenzylamine hydrochloride, N-(3-chloromethyl-benzyl)-N'-methylpiperazine dihydrochloride, N-(3-chloropropyl)-N-methylbenzylamine hydrochloride, in the same manner as described in Example 1-(1).

EXAMPLE 2

Compound 2

appearance: colorless oil

IR(neat, cm^{-1}): 2938, 1674, 1611, 1515, 1431, 1344, 1245, 1122, 1083, 1032, 753

High Resolution FAB-MS(m/z, $(C_{32}H_{38}N_2O_5+H)^+$):

Calcd.: 531.2859

Found : 531.2889

1H -NMR(300MHz, $CDCl_3$, δ ppm):

1.57(2H, brs), 1.75(2H, brs), 2.46(4H, brs), 2.64(1H, dd, $J=10.6$ Hz, 13.8Hz), 2.66-2.91(2H, m), 3.07(1H, dd, $J=2.7$ Hz, 13.8Hz), 3.13(1H, ddd, $J=5.4$ Hz, 11.2Hz, 13.3Hz), 3.46-3.72(2H, m), 3.75(3H, s), 3.88(3H, s), 3.93(3H, s), 4.29+5.69-5.77(1H, dd+m, $J=2.7$ Hz, 10.6Hz), 4.40(1H, ddd, $J=2.5$ Hz, 6.4Hz, 13.3Hz), 5.11 (1H, d, $J=11.3$ Hz), 5.24-5.31+5.34(1H, m+d, $J=11.3$ Hz), 6.39+6.45(1H, s \times 2), 6.64-6.76(4H, m), 7.17(1H, s), 7.34(3H, m), 7.41+7.97(1H, s \times 2)

EXAMPLE 3

Compound 3

appearance: colorless oil

FAB-MS (m/z, $(C_{32}H_{38}N_2O_5+H)^+$): 547

IR(neat, cm^{-1}): 2938, 1677, 1608, 1518, 1458, 1431, 1269, 1179, 1119, 1083, 1032, 1008

1H -NMR(300MHz, $CDCl_3$, δ ppm):

2.38+2.41-2.47(4H, t+m, $J=4.7$ Hz), 2.64(1H, dd, $J=10.7$ Hz, 13.5Hz), 2.72-2.90(2H, m), 3.06(1H, dd, $J=2.8$ Hz, 13.5Hz), 3.10-3.30+4.40(2H, m+ddd, $J=2.5$ Hz, 4.0Hz, 13.0Hz), 3.44+3.48(2H, d \times 2, $J=13.5$ Hz, $J=13.5$ Hz), 3.64+3.65-4.00(4H, t+m, $J=4.7$ Hz), 3.74+3.75(3H, s \times 2), 3.86+3.88(3H, s \times 2), 3.93(3H, s), 4.28+5.72(1H, ddx 2, $J=2.5$ Hz, 10.8Hz, $J=4.2$ Hz, 10.8Hz), 5.13(1H, d, $J=11.3$ Hz), 5.26+5.33(1H, d \times 2, $J=11.3$ Hz, $J=11.3$ Hz), 6.39+6.46(1H, s \times 2), 6.67-6.85 (4H, m), 7.17(1H, s), 7.33-7.37(3H, m), 7.38+7.97(1H, s \times 2)

EXAMPLE 4

Compound 4

appearance: pale yellow oil

High Resolution FAB-MS(m/z, $(C_{30}H_{38}N_2O_5+H)^+$):

Calcd.: 505.2702

Found : 505.2719

1H -NMR(300MHz, $CDCl_3$, δ ppm):

2.25+2.28(6H, s \times 2), 2.66(1H, dd, $J=10.7$ Hz, 13.9Hz), 2.71-2.92(2H, m), 3.08(1H, dd, $J=2.7$ Hz, 13.9Hz), 3.13-

3.30(1H,m),3.46+3.49(2H,s × 2),3.74+3.75(3H,s × 2),3.86+3.88(3H,s × 2),3.93(3H,s),4.35+5.70-5.77 (1H, dd+m,J=2.7Hz,10.7Hz),4.36-4.45(1H,m),5.11+ 5.12(1H,d × 2,1=11.1Hz,J=11.1Hz),5.24+5.33(1H,d × 2,J=11.1Hz,J=11.1Hz),6.39+6.46(1H,s × 2),6.67-6.90(4H,m),7.22+7.97(1H,s × 2),7.34(2H,d, J=8.2Hz),7.42(2H, d,J=8.2Hz)

5

EXAMPLE 5

Compound 5

10 appearance: colorless oil

IR(neat, cm⁻¹): 2938,2800,1677,1518,1497,1458,1428, 1248,1122,1083,1032,825,753

High Resolution FAB-MS (m/z, (C₃₃H₄₁N₃O₅+H)⁺):

Calcd.: 560.3124

Found : 560.3134

15 ¹H-NMR(300MHz, CDCl₃, δppm):

2.22-2.56(8H,m),2.27(3H,s),2.64(1H,dd,J=10.6Hz, 14.0Hz),2.72(1H,ddd,J=2.2Hz,5.3Hz,16.8Hz),2.85 (1H,ddd,J=6.3Hz,10.9Hz,16.8Hz),3.06(1H,dd, J=2.6Hz,14.0Hz),3.14(1H,ddd,J=5.3Hz,10.9Hz, 12.8Hz),3.21-3.31+4.40(1H,m+ddd,J=2.2Hz,6.3Hz, 12.8Hz),3.40-3.56(2H,m),3.75(3H,s),3.88(3H,s), 3.93(3H,s),4.29+5.69-5.75(1H,dd+m,J=2.6Hz, 10.6Hz),5.12(1H,d,J=11.1Hz),5.22-5.28+5.33(1H, m+d,J=11.1Hz),6.39+6.46(1H,s × 2),6.64-6.86(4H, m),7.18(1H,s),7.24-7.51(3H,m),7.38+7.97(1H,s × 2)

20

EXAMPLE 6

Compound 6

25

appearance: colorless oil

IR(neat, cm⁻¹): 2944,2840,2796,1676,1606,1586,1516, 1498, 1458, 1432, 1248, 1122, 1034, 738

FAB-MS (m/z, (C₃₁H₃₈N₂O₅+H)⁺): 519

¹ H-NMR(300MHz, CDCl₃, δppm):

30 2.06-2.15(2H,m),2.24+2.25(3H,s × 2),2.65(2H,brt, J=7.3Hz),2.76(1H,dd,J=10.5Hz,13.9Hz),2.70-2.92 (2H,m),3.14(1H,dd,J=2.8Hz,13.9Hz),3.17-3.25(1H, m),3.54(2H,s),3.75+3.77(3H,s × 2),3.84(3H,s),3.85 (3H,s), 4.14-4.21(1H,m),4.34-4.48(2H,m),4.62+5.73 (1H,dd × 2,1=2.8Hz,10.5Hz,J=4.2Hz,9.8Hz),6.35+ 6.42(1H,s × 2),6.75-6.85(2H,m),7.00-7.07(2H,m), 7.22-7.33(5H,m),7.51+8.00(1H,s × 2)

35

Compounds 7~12 (Examples 7~12) were prepared by the reaction of intermediate 2 (Referential Example 2) with the corresponding chlorides, 3-chloromethyl-N,N-dimethylbenzylamine hydrochloride, 4-chloromethyl-N,N-dimethylbenzylamine hydrochloride, 3-chloromethyl-4-methoxy-N,N-dimethylbenzylamine hydrochloride, N-(3-chloromethylbenzyl)morpholine hydrochloride, 2-chloro-methylpyridine hydrochloride, 3-chloromethylpyridine hydrochloride in the same manner as described in Example 1-(1).

40

EXAMPLE 7

Compound 7

45

appearance: pale yellow oil

IR(neat, cm⁻¹): 3466,2776,1605,1497,1437,1344,1236, 1122,1032,800,703

High Resolution FAB-MS (m/z, (C₃₀H₃₈N₂O₅+H)⁺):

Calcd.: 505.2702

Found : 505.2730

¹H-NMR(300MHz, CDCl₃, δppm):

50 2.22+2.29(6H,s × 2),2.70(1H,dd,J=10.7Hz,13.8Hz), 2.68-2.91(2H,m),3.12(1H,dd,J=2.8Hz,13.8Hz),3.11-3.18(1H,m),3.42(1H,d,J=13.1Hz),3.48(1H,d, J=13.1Hz),3.67+3.70(3H,s × 2),3.86+3.88(3H,s × 2), 3.92(3H,s), 4.35-4.42(2H,m),5.11+5.14(1H,d × 2, J=10.1Hz,J=11.2Hz),5.28+5.33(1H,d × 2,1=10.1Hz, J=11.2Hz),6.40+6.46(1H,s × 2),6.44+6.46(1H,s × 2), 6.69-6.72(1H,m),7.07-7.10(1H,m),7.23(1H,s),7.29-7.47(4H,m),7.39+7.92 (1H,s × 2)

55

EXAMPLE 8

Compound 8

- 5 appearance: colorless oil
 IR(neat, cm^{-1}): 2944, 2776, 1677, 1605, 1584, 1497, 1458, 1437, 1122, 1083, 1035, 966
 High Resolution FAB-MS(m/z , $(\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_5\text{H})^+$):
 Calcd.: 505.2702
 Found : 505.2713
- 10 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):
 2.24+2.28(6H, s \times 2), 2.71(1H, dd, $J=10.7\text{Hz}$, 13.8Hz), 2.70-2.89(2H, m), 3.13(1H, dd, $J=2.5\text{Hz}$, 13.8Hz), 3.12-3.20(1H, m), 3.46(2H, brs), 3.68+3.71(3H, s \times 2), 3.86+3.88(3H, s \times 2), 3.92(3H, s), 4.35-4.43(1H, m), 4.43(1H, dd, $J=2.5\text{Hz}$, 10.7Hz), 5.15(1H, d, $J=11.1\text{Hz}$), 5.31(1H, d, $J=11.1\text{Hz}$), 6.40+6.44(1H, s \times 2), 6.44-6.59 (2H, m), 6.67-6.72(1H, m), 7.07-7.13(1H, m), 7.29-7.42 (4H, m), 7.42+7.98(1H, s \times 2)

EXAMPLE 9

Compound 9

- 20 appearance: colorless oil
 IR(neat, cm^{-1}): 2944, 2776, 1674, 1605, 1584, 1500, 1461, 1437, 1260, 1122, 1083, 1032, 756
 High Resolution FAB-MS(m/z , $(\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_6+\text{H})^+$):
 Calcd.: 535.2808
 Found : 535.2828
- 25 $^1\text{H-NMR}$ (300mHz, CDCl_3 , δ ppm):
 2.20+2.30(6H, s \times 2), 2.67(1H, dd, $J=10.7\text{Hz}$, 13.6Hz), 2.70-2.89(2H, m), 3.13(1H, dd, $J=2.5\text{Hz}$, 13.6Hz), 3.10-3.19(1H, m), 3.40(2H, brs), 3.67+3.71(3H, s \times 2), 3.74 (3H, s), 3.85+3.87(3H, s \times 2), 3.91+3.95(3H, s \times 2), 4.36-4.43(1H, m), 4.54(1H, dd, $J=2.5\text{Hz}$, 10.7Hz), 5.14 (1H, d, $J=10.9\text{Hz}$), 5.42(1H, d, $J=10.9\text{Hz}$), 6.37+6.43 (1H, s \times 2), 6.43-6.54(2H, m), 6.68-6.71(1H, m), 8.67 (1H, d, $d=8.1\text{Hz}$), 7.05-7.13(1H, m), 7.27-7.29(2H, m), 7.43+7.98(1H, s \times 2)

EXAMPLE 10

Compound 10

- 35 appearance: colorless oil
 IR(neat, cm^{-1}): 2938, 2854, 1677, 1605, 1584, 1497, 1458, 1434, 1269, 1119, 864, 753
 High Resolution FAB-ms(m/z , $(\text{C}_{32}\text{H}_{38}\text{N}_2\text{O}_6+\text{H})^+$):
 calcd.: 547.2808
 Found : 547.2781
- 40 $^1\text{H-NMR}$ (300mHz, CDCl_3 , δ ppm):
 2.37+2.43(4H, brt \times 2, $1=4.6\text{Hz}$, $1=4.6\text{Hz}$), 2.69(1H, dd, $J=10.9\text{Hz}$, 13.6Hz), 2.71-3.00(2H, m), 3.11(1H, dd, $J=2.4\text{Hz}$, 13.6Hz), 3.10-3.19(1H, m), 3.43(1H, d, $J=3.2\text{Hz}$), 3.49(1H, d, $J=3.2\text{Hz}$), 3.64-3.69(4H, m), 3.71 (3H, s), 3.86+3.88(3H, s \times 2), 3.93(3H, s), 4.32-4.42 (2H, m), 5.16(1H, d, $J=11.3\text{Hz}$), 5.32(1H, d, $J=11.3\text{Hz}$), 6.40-6.55(3H, m), 6.69-6.72(1H, m), 7.07-7.13(1H, m), 7.20(1H, s), 7.31-7.38(3H, m), 7.38+7.98(1H, s \times 2)

EXAMPLE 11

Compound 11

- 50 appearance: colorless oil
 IR(neat, cm^{-1}): 2944, 1674, 1605, 1497, 1458, 1437, 1344, 1269, 1122, 1086, 1038, 762
 High Resolution FAB-MS(m/z , $(\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_5+\text{H})^+$):
 Calcd.: 449.2076
 Found : 449.2091
- 55 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):
 2.76(1H, dd, $J=10.9\text{Hz}$, 13.8Hz), 2.73-2.95(2H, m), 3.14-3.24(2H, m), 3.68+3.71(3H, s \times 2), 3.86+3.87(3H, s \times 2), 3.91(3H, s), 4.41(1H, ddd, $J=2.7\text{Hz}$, 6.6Hz, 13.2Hz), 4.71(1H, dd, $J=2.8\text{Hz}$, 10.9Hz), 5.27+5.29(1H, d \times 2, $J=12.1\text{Hz}$, $1=12.7\text{Hz}$), 5.40+5.45(1H, d \times 2, $J=12.7\text{Hz}$, $1=12.1\text{Hz}$), 6.42+6.47(1H, s \times 2), 6.51-6.59 (2H, m), 6.69-6.73(1H, m),

7.08-7.14(1H,m),7.26-7.30 (1H,m),7.41+7.99(1H,s × 2),7.51-7.54(1H,m),7.72-7.77(1H,m),8.63-8.65(1H,m)

EXAMPLE 12

5 Compound 12

appearance: colorless oil

IR(neat, cm⁻¹): 2944,1674,1605,1584,1497,1434,1344, 1267,1233,1122,1086,1032

High Resolution FAB-MS(m/z, (C₂₈H₂₈N₂O₅+H)⁺):

10 Calcd.: 449.2076

Found : 449.2077

¹H-NMR(300MHz, CDCl₃, δ ppm):

2.59-2.91(2H,m),2.76(1H,dd,J=10.5Hz,13.9Hz),3.10 (1H,dd,J=2.9Hz,13.9Hz),3.13-3.29(1H,m),3.69+3.71
(3H,s × 2),3.86+3.90(3H,s × 2),3.86+3.88(3H,s × 2), 4.37-4.45(1H,m),4.47+5.76(1H,dd × 2,J=2.9Hz, 10.5Hz,
15 J=4.3Hz,9.2Hz),5.13+5.20(1H,d × 2, J=11.4Hz,J=11.6Hz),5.25+5.34(1H,d × 2,J=11.4Hz, J=11.6Hz),6.43+6.49
(1H,s × 2),6.51-6.58(2H,m), 6.69-6.74(1H,m),7.09+7.14(1H,t × 2,1=7.9Hz, J=7.8Hz),7.32-7.38(1H,m),7.37+
8.00(1H,s × 2), 7.79+7.90-7.94(1H,td+m,J=2.1Hz,7.8Hz),8.61-8.64 (1H,m),8.74-8.75(1H,m)

Compounds 13~21 (Examples 13~21) were prepared by the reaction of corresponding intermediates 3~9
(Referential Examples 3~9) with the corresponding chlorides, 3-chloromethyl-N,N-dimethylbenzylamine hyd-
20 rochloride, N-(3-chloromethylbenzyl)morpholine hydrochloride, (4-chlorobutylthio)benzene, in the same man-
ner as described in Example 1-(1).

EXAMPLE 13

25 Compound 13

appearance: pale brown oil

IR(neat, cm⁻¹): 2944,1674,1605,1500,1464,1434,1344, 1245,1122,1086,1032,753

High Resolution FAB-MS(m/z, (C₃₀H₃₈N₂O₅+H)⁺):

30 calcd.: 505.2705

Found : 505.2704

¹H-NMR(300MHz, CDCl₃, δppm):

2.21+2.27(6H,s × 2),2.77-2.83(2H,m),3.23(2H,d, J=6.3Hz),3.25-3.38(1H,m),3.41(1H,d,J=13.1Hz), 3.46
(1H,d,J=13.1Hz),3.64+3.67(3H,s × 2),3.86+3.88 (3H,s × 2),3.86+3.90(3H,s × 2),4.23-4.30(1H,m), 4.53(1H,
35 t,J=7.2Hz),5.15(1H,d,J=11.3Hz),5.30(1H, d,J=11.3Hz),6.41+6.47(1H,s × 2),6.72-6.79(3H,m), 7.12-7.18(1H,m),
7.29-7.40(5H,m)

EXAMPLE 14

40 Compound 14

appearance: colorless oil

IR(neat, cm⁻¹): 3466,2944,1668,1518,1500,1458,1431, 1269,1239,1122,1029

High Resolution FAB-MS(m/z, (C₃₁H₃₈N₂O₆+H)⁺):

45 Calcd.: 535.2808

Found : 535.2838

¹H-NMR(300MHz, CDCl₃, δppm):

2.21+2.29(6H,s × 2),2.70(1H,dd,1=10.4Hz,14.0Hz), 2.68-2.94(2H,m),3.07(1H,dd,J=2.8Hz,14.0Hz),3.11-
3.19(1H,m),3.41(1H,d,J=13.5Hz),3.45(1H,d, J=13.5Hz),3.65+3.67(3H,s × 2),3.82+3.83(3H,s × 2), 3.85+3.88
50 (3H,s × 2),3.93(3H,s),4.36-4.43(2H,m), 5.16(1H,d,J=11.5Hz),5.33(1H,d,J=11.5Hz),6.46-6.52(3H,m),6.65-6.70
(1H,m),7.28-7.50(4H,m), 7.37+8.01(1H,s × 2)

EXAMPLE 15

55 Compound 15

appearance: colorless oil

IR(neat, cm⁻¹): 2944,2836,1671,1608,1506,1432,1227, 1122,1083,1032,790,745,695

High Resolution FAB-MS(m/z, (C₃₁H₃₈N₂O₆+H)⁺):

Calcd.: 535.2808

Found : 535.2825

¹H-NMR(300MHz, CDCl₃, δppm):

5 2.01+2.28(6H,s × 2), 2.70-2.91(2H,m), 3.01(2H,d, J=7.1Hz), 3.28(1H,ddd, J=6.3Hz, 10.0Hz, 13.4Hz), 3.45
(1H,d, J=13.0Hz), 3.47(1H,d, J=13.0Hz), 3.61+3.63 (3H,s × 2), 3.63+3.66(3H,s × 2), 3.85+3.88(3H,s × 2), 3.88+
3.90(3H,s × 2), 4.25(1H,ddd, J=3.5Hz, 6.3Hz, 13.4Hz), 4.54+5.89(1H,t+dd, J=7.1Hz, J=3.8Hz, 10.0Hz), 5.17+5.18
(1H,d × 2, J=11.2Hz, J=11.2Hz), 5.27+5.28(1H,d × 2, J=11.2Hz, J=11.2Hz), 6.41+6.46 (1H,s × 2), 6.47(1H,s),
6.60-6.75(2H,m), 7.24-7.55 (4H,m), 7.38+7.92(1H,s × 2)

10

EXAMPLE 16

Compound 16

15 appearance: yellow oil

High Resolution FAB-MS(m/z, (C₃₂H₄₀N₂O₇+H)⁺):

Calcd.: 565.2914

Found : 565.2920

¹H-NMR(300MHz, CDCl₃, δppm):

20 2.21+2.34(6H,s × 2), 2.73(1H,dd, J=10.5Hz, 13.9Hz), 2.79-3.01(2H,m), 3.06(1H,dd, J=2.6Hz, 13.9Hz), 3.10-
3.27(1H,m), 3.43(2H,s), 3.68(6H,s), 3.78+3.79(3H,s × 2), 3.87+3.88(3H,s × 2), 3.92(3H,s), 4.37-4.48(1H, m), 4.41-
4.48+5.75-5.82(1H,m × 2), 5.11+5.18(1H,d × 2, J=11.5Hz, J=11.5Hz), 5.27+5.32(1H,d × 2, J=11.5Hz, J=11.5Hz),
6.13+6.17(2H,s × 2), 6.40+6.47(1H,s × 2), 7.26-7.55(4H,m), 7.39+8.06(1H,s × 2)

25 EXAMPLE 17

Compound 17

appearance: pale yellow oil

30 IR(neat, cm⁻¹): 2944, 1674, 1497, 1458, 1434, 1344, 1122, 1086, 1029

High Resolution FAB-MS(m/z, (C₂₈H₃₃N₃O₄ +H)⁺):

Calcd.: 476.2549

Found : 476.2520

¹H-NMR(300MHz, CDCl₃, δppm):

35 2.18+2.24(6H,s × 2), 2.60-2.95(2H,m), 2.73(1H,dd, J=10.7Hz, 13.9Hz), 3.14(1H,dd, J=2.6Hz, 13.9Hz), 3.15-
3.40(1H,m), 3.40+3.47(2H,s × 2), 3.86+3.88(3H, s × 2), 3.90+3.94(3H,s × 2), 4.31+5.71(1H,dd × 2, J=2.6Hz,
10.7Hz, J=2.8Hz, 9.0Hz), 4.38-4.50(1H,m), 5.09+5.13(1H,d × 2, J=10.5Hz, J=10.5Hz), 5.31+5.36 (1H,d × 2, J=10.5Hz,
J=10.5Hz), 6.41+6.46(1H,s × 2), 7.00-7.61(8H,m), 7.60+7.95(1H,s × 2)

40 EXAMPLE 18

Compound 18

appearance: colorless oil

45 IR(neat, cm⁻¹): 2944, 2775, 1671, 1611, 1515, 1434, 1344, 1245, 1122, 1086, 1032, 827

High Resolution FAB-MS(m/z, (C₃₁H₃₈N₂O₅+H)⁺):

Calcd.: 519.2859

Found : 519.2830

¹H-NMR(300MHz, CDCl₃, δppm):

50 1.78-1.94+2.15-2.45(2H,m × 2), 2.21+2.30(6H,s × 2), 2.48-3.11(5H,m), 3.43+3.57(2H,s × 2), 3.75+3.78
(3H, s × 2), 3.82+3.84(3H,s × 2), 3.83+3.87(3H,s × 2), 4.22+5.59(1H,dd × 2, J=3.0Hz, 10.9Hz, J=3.0Hz, 10.7Hz),
4.40(1H,ddd, J=2.5Hz, 6.8Hz, 12.8Hz), 5.04-5.21(2H,m), 6.38+6.40(1H,s × 2), 6.74+6.77(2H,d × 2, J=8.3Hz, J=
8.8Hz), 6.97+7.00(2H,d × 2, J=8.3Hz, J=8.8Hz), 7.11-7.45(4H,m), 7.73+8.22(1H,s × 2)

55

EXAMPLE 19

Compound 19

5 appearance: colorless oil
 IR(neat, cm^{-1}): 2944, 2780, 1674, 1479, 1440, 1389, 1263, 1155, 1095, 1038, 695
 High Resolution FAB-MS(m/z , $(\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_5+\text{H})^+$):
 Calcd.: 489.2389
 Found : 489.2408
 10 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):
 2.26+2.32(6H, s \times 2), 2.54-2.92(3H, m), 3.06-3.34(2H, m), 3.54+3.64(2H, s \times 2), 3.68+3.69(3H, s \times 2), 3.43-
 3.52+4.39(1H, m+ddd, $J=2.4\text{Hz}$, 6.3Hz, 13.2Hz), 4.58+5.81(1H, dd \times 2, $J=10.4\text{Hz}$, 12.4Hz, $J=3.8\text{Hz}$, 9.4Hz), 5.32+5.33
 (1H, d \times 2, $J=11.4\text{Hz}$, $J=11.2\text{Hz}$), 5.39+5.42(1H, d \times 2, $J=11.4\text{Hz}$, $J=11.2\text{Hz}$), 5.92+5.96 (1H, d+s, $J=3.0\text{Hz}$), 5.95+
 5.96(1H, d+s, $J=3.0\text{Hz}$), 6.30+6.37(1H, s \times 2), 6.46-6.76(3H, m), 7.03-7.50(5H, m), 7.40+7.97(1H, s \times 2)

EXAMPLE 20

Compound 20

20 appearance: colorless oil
 IR(neat, cm^{-1}): 2944, 2812, 1677, 1626, 1482, 1440, 1263, 1155, 1116, 1038, 864, 753
 High Resolution FAB-MS(m/z , $(\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_6+\text{H})^+$):
 Calcd.: 531.2495
 Found : 531.2500
 25 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):
 2.38(4H, t, $J=4.6\text{Hz}$), 2.51-2.90(3H, m), 3.08-3.35(2H, m), 3.48(2H, s), 3.64(4H, t, $J=4.6\text{Hz}$), 3.65+3.68(3H, s
 \times 2), 4.39(1H, ddd, $J=2.8\text{Hz}$, 6.6Hz, 13.1Hz), 4.56+5.79 (1H, dd \times 2, $J=2.6\text{Hz}$, 10.5Hz, $J=4.0\text{Hz}$, 9.4Hz), 5.30+ 5.33
 (1H, d \times 2, $J=11.4\text{Hz}$, $J=11.3\text{Hz}$), 5.39+5.42(1H, d \times 2, $J=11.4\text{Hz}$, $J=11.3\text{Hz}$), 5.93+5.97(1H, d+s, $J=6.3\text{Hz}$), 5.94+
 5.97(1H, d+s, $J=6.3\text{Hz}$), 6.30+6.37(1H, s \times 2), 6.46-6.76(3H, m), 7.10(1H, t, $J=8.0\text{Hz}$), 7.39-7.48(4H, m), 7.43+7.96
 30 (1H, s \times 2)

EXAMPLE 21

Compound 21

35 appearance: pale yellow oil
 IR(neat, cm^{-1}): 1605, 1404, 1311, 1272, 1236, 1191, 1026, 717, 693
 High Resolution FAB-MS(m/z , $(\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_4\text{S}+\text{H})^+$):
 Calcd.: 493.2161
 Found : 493.2151
 40 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):
 1.80-2.10(4H, m), 2.55-2.65+2.69-2.80(1H, m \times 2), 2.87(1H, dd, $J=10.5\text{Hz}$, 14.2Hz), 2.80-3.02(1H, m), 3.00-
 3.10(2H, m), 3.22+3.24(1H, dd \times 2, $J=4.2\text{Hz}$, 14.2Hz, $J=4.2\text{Hz}$, 14.2Hz), 3.40-3.62(1H, m), 3.81+3.82 (3H, s \times 2), 3.84+
 3.85(3H, s \times 2), 4.00-4.16(1H, m), 4.20-4.40(1H, m), 4.46(1H, ddd, $J=2.4\text{Hz}$, 6.9Hz, 13.2Hz), 4.67+5.71(1H, dd \times
 45 2, $J=4.2\text{Hz}$, 10.5Hz, $J=4.2\text{Hz}$, 10.5Hz), 6.38+6.43(1H, s \times 2), 7.12-7.56(7H, m), 7.60+7.99(1H, s \times 2), 8.26+8.45(1H,
 d, $J=1.8\text{Hz}$, $J=1.8\text{Hz}$), 8.44+8.51(1H, dd, $J=1.8\text{Hz}$, 4.9Hz, $J=1.8\text{Hz}$, 4.9Hz)

EXAMPLE 22

50 (1) Preparation of 8-(3-chloromethylbenzyloxy)-2-formyl-6,7-dimethoxy-1-(3-methoxybenzyl)-1,2,3,4-tet-
 rahydroisoquinoline

To a suspension of sodium hydride (80 mg, 1.96 mmole, 60%) in dimethyl sulfoxide (1 ml) was added a
 solution of intermediate 2 obtained in Referential Example 2 (350 mg, 0.98 mmole) at room temperature under
 55 nitrogen, and the reaction mixture was stirred for 10 minutes. The resulting mixture was added dropwise to a
 solution of α, α' -dichloro-m-xylene (172 mg, 0.98 mmole) in dimethyl sulfoxide (1 ml) at room temperature, and
 stirred for 2 hours. The reaction mixture was chilled in ice, diluted with water, and extracted with ethyl acetate.
 The combined organic layers were dried over MgSO_4 , and concentrated under reduced pressure. The residue

was purified by column chromatography (silica gel/ethyl acetate) to give the desired compound (387 mg) as a pale yellow oil.

FAB-MS (m/z, (C₂₈H₃₀N₅O₅Cl+H)⁺): 496

5 (2) Preparation of Compound 22

The compound obtained in (1) (64.0 mg, 0.129 mmole) was treated with a 40% solution of methylamine in methanol (2 ml), and stirred at room temperature for 4 hours. The mixture was evaporated under reduced pressure, and the residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloro-
10 form:methanol=10:1) to give the captioned compound (51.2 mg) as a pale yellow oil.

IR(neat, cm⁻¹): 2938,2794,1674,1605,1584,1497,1458, 1437,1377,1344,1269,1236,1191,1151, 1122,1083, 1032,1005,963,753,699

High Resolution FAB-MS (m/z, (C₂₉H₃₄N₂O₅+H)⁺):

Calcd.: 491.2546

15 Found : 491.2540

¹H-NMR(300MHz, CDCl₃, δppm):

2.42+2.53(3H, s × 2), 2.63-2.91(3H, m), 3.07-3.20(2H, m), 3.53-3.60+4.34-4.42(1H, m × 2), 3.70+3.73(3H, s × 2), 3.88(2H, s), 3.81+3.87(3H, s × 2), 3.92+3.96(3H, s × 2), 4.34-4.42+5.37-5.42(1H, m × 2), 5.05+5.14(1H, d × 2, J=11.3Hz, J=11.3Hz), 5.33+5.42(1H, d × 2, J=11.3Hz, J=11.3Hz), 6.35-6.50(3H, m), 6.68-6.74(1H, m), 7.08-7.17(1H, m), 7.30-7.45(4H, m), 7.47+7.78(1H, s × 2)
20

Compounds 23~25 (Examples 23~25) were prepared by the reaction of the compound obtained in Example 22-(1) with the corresponding amines, N-methylpiperazine, thiomorpholine, 1,3-thiazolidine, in the same manner as described in Example 22-(2). Compounds 26~29 were prepared using intermediate 2 obtained in Referential Example 2, α,α'-dichloro-o-xylene and dimethylamine (Example 26); intermediate 1 obtained in Referential Example 1, α,α'-dichloro-o-xylene and dimethylamine (Example 27); intermediate 1, α,α'-dichloro-m-xylene and N-methylethanolamine (Example 28); intermediate 10 obtained in Referential Example 10, α,α'-dichloro-o-xylene and dimethylamine (Example 29), in the same manner as described in Example 22.
25

30 EXAMPLE 23

Compound 23

appearance: pale yellow oil

35 IR(neat, cm⁻¹): 2938,2800,1677,1605,1584,1497,1461, 1437,1374,1344,1269,1236,1188,1167, 1122,1086, 1035,1014,978,963,825, 753,699

High Resolution FAB-MS (m/z, (C₃₃H₄₁N₃O₅+H)⁺):

Calcd.: 560.3124

Found : 560.3143

40 ¹H-NMR(300MHz, CDCl₃, δppm):

2.29+2.31(3H, s × 2), 2.32-2.56(8H, m), 2.69(1H, dd, J=11.0Hz, 14.0Hz), 2.74-2.91(2H, m), 3.11(1H, dd, J=3.0Hz, 14.0Hz), 3.10-3.20(1H, m), 3.47+3.54(2H, s × 2), 3.70+3.73(3H, s × 2), 3.86+3.88(3H, s × 2), 3.93 (3H, s), 4.30-4.42(1H, m), 4.36+5.76-5.82(1H, dd+m, J=3.0Hz, 11.0Hz), 5.12+5.14(1H, d × 2, J=11.2Hz, J=11.2Hz), 5.26+5.32(1H, d × 2, J=11.2Hz, J=11.2Hz), 6.40-6.58(3H, m), 6.68-6.73(1H, m), 7.09+7.10(1H, t × 2, J=8.0Hz, J=8.0Hz),
45 7.20-7.50(4H, m), 7.37+7.98(1H, s × 2)

EXAMPLE 24

Compound 24

50

appearance: pale brown oil

IR(neat, cm⁻¹): 2938,1677,1605,1584,1497,1458,1434, 1371,1344,1266,1236,1191,1155,1122, 1083,1035, 1005,963,798,753,699

High Resolution FAB-MS(m/z, (C₃₂H₃₈N₂O₅S+H)⁺):

55 Calcd.: 563.2579

Found : 563.2597

¹H-NMR(300MHz, CDCl₃, δppm):

2.55-2.91(11H, m), 2.69(1H, dd, J=11.0Hz, 13.8Hz), 3.11(1H, dd, J=3.0Hz, 13.89Hz), 3.47+3.54(2H, s × 2),

3.67+3.70(3H,s × 2), 3.86+3.88(3H,s × 2), 3.93(3H, s), 4.34+5.75-5.81(1H,dd+m,J=3.0Hz,11.0Hz), 4.35-4.42(1H, m), 5.12+5.16(1H,d × 2, J=11.2Hz, J=11.2Hz), 5.26+5.32(1H,d × 2, J=11.2Hz, J=11.2Hz), 6.39-6.57 (3H,m), 6.65-6.73(1H,m), 7.06+7.10(1H,t × 2, J=7.7Hz, J=7.7Hz), 7.19-7.48(4H,m), 7.35+7.98(1H,s × 2)

5 EXAMPLE 25

Compound 25

appearance: pale yellow oil

10 IR(neat, cm⁻¹): 2944, 1674, 1605, 1563, 1497, 1434, 1374, 1344, 1266, 1233, 1155, 1122, 1083, 1044

High Resolution FAB-MS(m/z, (C₃₁H₃₈N₂O₅S+H)⁺):

Calcd.: 549.2423

Found : 549.2443

¹H-NMR(300MHz, CDCl₃, δppm):

15 2.70(1H,dd,J=10.7Hz,13.6Hz), 2.74-3.20(7H,m), 3.11 (1H,dd,J=2.0Hz,13.6Hz), 3.52+3.58(2H,s × 2), 3.67+3.71(3H,s × 2), 3.86+3.88(3H,s × 2), 3.93(3H,s), 3.96+4.04(2H,s × 2), 4.33-4.43+5.74-5.80(2H,m × 2), 5.13+5.16(1H,d × 2, J=11.2Hz, J=11.2Hz), 5.27+5.33 (1H,d × 2, J=11.2Hz, J=11.2Hz), 6.39-6.56(3H,m), 6.66-6.74(1H,m), 7.09+7.10(1H,t × 2, J=8.0Hz, J=8.0Hz), 7.20-7.23(1H,m), 7.33-7.42(3H,m), 7.44+7.97(1H,s × 2)

20 EXAMPLE 26

Compound 26

appearance: colorless powder

25 m.p.: 126~128°C

IR(neat, cm⁻¹): 1677, 1605, 1458, 1434, 1122, 1086, 1032

High Resolution FAB-MS(m/z, (C₃₀H₃₈N₂O₅+H)⁺):

Calcd.: 505.2702

Found : 505.2716

30 ¹H-NMR(300MHz, CDCl₃, δppm):

2.18+2.21(6H,s × 2), 2.72(1H,dd,J=11.0Hz,13.6Hz), 2.80-2.95(1H,m), 3.11(1H,dd,J=2.8Hz,13.6Hz), 3.10-3.24(1H,m), 3.38(1H,d,J=12.8Hz), 3.57(1H,d, J=12.8Hz), 3.40-3.60(1H,m), 3.65+3.66(3H,s × 2), 3.87+3.89(3H,s × 2), 3.87+3.92(3H,s × 2), 4.34-4.46+5.79(2H,m+dd,J=3.0Hz,6.7Hz), 5.22+5.24(1H,d × 2, J=11.8Hz, J=11.8Hz), 5.47+5.57(1H,d × 2, J=11.8Hz, J=11.8Hz), 6.37(1H,d,J=7.5Hz), 6.40(1H,d,J=2.4Hz), 6.47(1H,s), 6.69(1H,dd,J=2.4Hz,7.5Hz), 7.08(1H,t, J=7.5Hz), 7.30-7.41(3H,m), 7.507.58(1H,m), 7.36+7.98(1H,s × 2)

EXAMPLE 27

Compound 27

40 appearance: colorless oil

IR(neat, cm⁻¹): 2938, 2860, 2770, 1674, 1611, 1515, 1458, 1434, 1248, 1179, 1122, 1032, 843, 756

High Resolution FAB-MS(m/z, (C₃₀H₃₈N₂O₅+H)⁺):

Calcd.: 505.2702

45 Found : 505.2725

¹H-NMR(300MHz, CDCl₃, δppm):

2.20+2.25(6H,s × 2), 2.66(1H,dd,J=10.7Hz,13.9Hz), 2.70-2.84(2H,m), 3.05(1H,dd,J=2.9Hz,13.9Hz), 3.16(1H,ddd,J=5.4Hz,10.9Hz,13.2Hz), 3.42(1H,d, J=13.1Hz), 3.62(1H,d,J=13.1Hz), 3.74+3.75(3H,s × 2), 3.87+3.89(3H,s × 2), 3.93(3H,s), 4.33+5.70(1H,dd × 2, J=2.9Hz,10.7Hz, J=2.9Hz,10.7Hz), 4.40(1H,ddd, J=2.4Hz,6.3Hz, 13.2Hz), 5.21(1H,d,J=11.7Hz), 5.46+5.59(1H,d × 2, J=11.5Hz, J=11.7Hz), 6.41+6.47 (1H,s × 2), 6.61-6.83(4H, m), 7.27-7.72(4H,m), 7.22+7.98(1H,s × 2)

EXAMPLE 28

55 Compound 28

appearance: pale yellow oil

IR(neat, cm⁻¹): 1668, 1516, 1498, 1456, 1432, 1248, 1122, 1084, 1032

High Resolution FAB- m/z , ($C_{31}H_{38}N_2O_8+H$)⁺:

Calcd.: 535.2808

Found : 535.2829

¹H-NMR(300MHz, CDCl₃, δ ppm):

2.17+2.28(3H,s \times 2), 2.56(2H,t, $J=5.3$ Hz), 2.65(1H, dd, $J=10.8$ Hz, 13.9Hz), 2.50-2.92(2H,m), 3.05(1H, dd, $J=2.6$ Hz, 13.9Hz), 3.05-3.28(1H,m), 3.55+3.56(2H,s \times 2), 3.60(2H,t, $J=5.3$ Hz), 3.74+3.76(3H,s \times 2), 3.86+ 3.88(3H,s \times 2), 3.90+3.94(3H,s \times 2), 4.26+5.70(1H, dd \times 2, $J=2.6$ Hz, 10.8Hz, $J=4.3$ Hz, 13.5Hz), 4.39(1H, ddd, $J=2.3$ Hz, 6.4Hz, 13.1Hz), 5.08+5.13(1H,d \times 2, $J=10.7$ Hz, $J=11.1$ Hz), 5.30+5.33(1H,dx 2, $J=10.7$ Hz, 11.1Hz), 6.40+6.46(1H, s \times 2), 6.65-6.83(4H,m), 7.16 (1H,s), 7.29-7.41(3H,m), 7.38+7.96(1H,s \times 2)

EXAMPLE 29

Compound 29

appearance: colorless oil

IR(neat, cm⁻¹): 2944, 2776, 1677, 1602, 1467, 1434, 1344, 1206, 1155, 1122, 840, 753

High Resolution FAB-MS(m/z , ($C_{31}H_{38}N_2O_8+H$)⁺):

Calcd.: 535.2808

Found : 535.2833

¹H-NMR(300MHz, CDCl₃, δ ppm):

2.17+2.22(6H,s \times 2), 2.70(1H, dd, $J=10.8$ Hz, 13.6Hz), 2.72-2.92(2H,m), 3.09(1H, dd, $J=2.8$ Hz, 13.6Hz), 3.13-3.21(1H,m), 3.38(1H,d, $J=12.8$ Hz), 3.54(1H,d, $J=12.8$ Hz), 3.63(6H,s), 3.88(3H,s), 3.91(3H,s), 4.33-4.41(1H,m), 4.45(1H, dd, $J=2.8$ Hz, 10.8Hz), 5.22+5.27 (1H,d \times 2, $J=11.7$ Hz, $J=12.2$ Hz), 6.04+6.13(2H,d \times 2, $J=2.2$ Hz, $J=2.1$ Hz), 6.24-6.26(1H,m), 6.42+6.47(1H,s \times 2), 7.28-7.34(4H,m), 7.35+8.00(1H,s \times 2), 7.53-7.56(1H,m)

EXAMPLE 30

(1) Preparation of 6,7-dimethoxy-8-(3-dimethylamino-methylbenzyloxy)-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline

To a solution of compound 1 obtained in Example 1 (268 mg, 0.531 mmole) in ethanol (4.6 ml) was added a solution of sodium hydroxide (500 mg, 12.5 mmole) in water (0.6 ml), and the reaction mixture was refluxed under an argon atmosphere for 22 hours. The reaction mixture was diluted with water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure to give the desired compound (213 mg) as a yellow oil.

FAB- m/z , ($C_{29}H_{36}N_2O_4+H$)⁺: 477

(2) Preparation of Compound 30

To a solution of the compound obtained in (1) (250 mg, 0.525 mmole) in dichloromethane (7 ml) were sequentially added hydroxyacetic acid (44 mg, 0.578 mmole), HOBt (78 mg, 0.577 mmole), and at 0°C EDCI (111 mg, 0.579 mmole), then the mixture was stirred under nitrogen at 0°C for 3.5 hours. To the mixture were added hydroxyacetic acid (34 mg, 0.447 mmole) and EDCI (82 mg, 0.428 mmole), and the reaction mixture was stirred at 0°C for 1.5 hours. The resulting mixture was roughly purified by dry column flash chromatography (silica gel/chloroform:methanol=10:1), and purified by preparative thin-layer chromatography (merck, silica gel 60F254/chloroform:methanol=10:1) to give the captioned compound (182 mg) as a colorless oil.

IR(neat, cm⁻¹): 2944, 1647, 1611, 1515, 1500, 1458, 1344, 1248, 1122, 1083, 1032

High Resolution FAB-MS(m/z , ($C_{31}H_{38}N_2O_8+H$)⁺):

Calcd.: 535.2808

Found : 535.2820

¹H-NMR(300MHz, CDCl₃, δ ppm):

2.31+2.46(6H,s \times 2), 2.70(1H,d, $J=15.0$ Hz), 2.65-3.51 (5H,m), 3.43(1H,d, $J=15.0$ Hz), 3.58+3.80(2H,s \times 2), 3.75(3H,s), 3.86+3.88(3H,s \times 2), 3.88+3.93(3H,s \times 2), 4.40+5.86(1H, dd \times 2, $J=1.8$ Hz, 10.7Hz, $J=5.4$ Hz, 8.3Hz), 4.65-4.75(1H,m), 5.05+5.08(2H,d \times 2, $J=11.1$ Hz, $J=11.1$ Hz), 5.24+5.41(1H,d \times 2, $J=11.1$ Hz, $J=11.1$ Hz), 6.40+6.45(1H,s \times 2), 6.63-6.78(4H,m), 7.40-7.55(4H,m)

Compounds 31~33 (Examples 31~33) were prepared by the condensation of the compound obtained in Example 30-(1) with the corresponding carboxylic acids, 3-hydroxypropionic acid, DL-lactic acid, methoxyacetic acid using tetrahydrofuran, dimethylformamide, dichloro-methane as solvents, in the same manner as described

in Example 30-(2).

EXAMPLE 31

5 Compound 31

appearance: pale yellow oil

IR(neat, cm^{-1}): 1743, 1638, 1515, 1464, 1437, 1344, 1248, 1179, 1122, 1092, 1032

High Resolution FAB-MS(m/z , $(\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_6+\text{H})^+$):

10 Calcd.: 549.2965

Found : 549.2985

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

2.21+2.22+2.23+2.26(6H,s \times 4), 2.20-3.60(11H,m), 3.74+3.75(3H,s \times 2), 3.86+3.88(3H,s \times 2), 3.92+3.94
 (3H,s \times 2), 4.20-4.40(1H,m), 4.62-4.82+5.93-6.05 (1H,m \times 2), 5.07+5.14(1H,d \times 2, J=11.2Hz, J=11.2Hz), 5.38+
 15 5.41(1H,d \times 2, J=11.2Hz, J=11.2Hz), 6.41+6.46 (1H,s \times 2), 6.65-6.85(4H,m), 7.30-7.50(4H,m)

EXAMPLE 32

20 Compound 32

appearance: pale yellow oil

IR(neat, cm^{-1}): 1644, 1515, 1497, 1458, 1248, 1122, 1089, 1032

High Resolution FAB-MS(m/z , $(\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_6+\text{H})^+$):

25 Calcd.: 549.2965

Found : 549.2985

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

0.43+0.96+1.01+1.26(3H,d \times 4, J=6.6Hz, J=6.6Hz, J=6.6Hz, J=6.6Hz), 2.24+2.28+2.33(6H,s \times 3), 2.50-
 3.10(4H,m), 3.13-3.70(4H,m), 3.74+3.86(3H,s \times 2), 3.86+3.87(3H,s \times 2), 3.88+3.89+3.92(3H,s \times 3), 4.96+ 5.03+
 5.08+5.12(1H,d \times 4, J=11.0Hz, J=11.0Hz, J=11.0Hz, J=11.0Hz), 5.20+5.30+5.42+5.46(1H,d \times 4, J=11.0Hz, J=
 30 11.0Hz, J=11.0Hz, J=11.0Hz), 4.75+4.88+ 5.88+5.99(1H,dd \times 4, J=10.9Hz, 3.0Hz, J=9.1Hz, 2.4Hz, J=7.9Hz, 5.5Hz,
 J=9.7Hz, 4.2Hz), 4.28-4.45+4.61-4.72 (1H,m \times 2), 6.41+6.43+6.47(1H,s \times 3), 6.63-6.87(4H, m), 7.30-7.60(4H,m)

EXAMPLE 33

35 Compound 33

appearance: yellow oil

IR(neat, cm^{-1}): 2938, 2824, 2776, 1659, 1611, 1584, 1518, 1500, 1458, 1368, 1344, 1305, 1248, 1179, 1122, 1089,
 1032

40 High Resolution FAB-MS(m/z , $(\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_6+\text{H})^+$):

Calcd.: 549.2965

Found : 549.2986

$^1\text{H-NMR}$ (300mHz, CDCl_3 , δ ppm):

2.26+2.31(6H,s \times 2), 2.50-3.10(4H,m), 2.80(1H,d, J=14.2Hz), 3.02(3H,s), 3.14-3.27(1H,m), 3.35(1H,d, J=
 45 14.2Hz), 3.48(2H,s), 3.73+3.74(3H,s \times 2), 3.86+ 3.88(3H,s \times 2), 3.87+3.93(3H,s \times 2), 4.70-4.82(1H, m), 4.70-
 4.82+5.95-6.02(1H,m \times 2), 5.03+5.05(1H,d \times 2, J=10.7Hz, J=10.7Hz), 5.22+5.39(1H,d \times 2, J=10.7Hz, J=10.7Hz),
 6.41+6.46(1H,s \times 2), 6.65-6.88(4H,m), 7.30-7.52(4H,m)

EXAMPLE 34

50

(1) Preparation of 6,7-dimethoxy-8-(3-dimethylamino-methylbenzyloxy)-1-(3-methoxybenzyl)-1,2,3,4-tet-
 rahydroisoquinoline

The desired compound was prepared as a yellow oil (yield: 622 mg) using compound 7 obtained in Example
 55 7 (772 mg, 1.53 mmole), in the same manner as described in Example 30-(1).

FAB-MS (m/z , $(\text{C}_{29}\text{H}_{38}\text{N}_2\text{O}_4+\text{H})^+$): 477

(2) Preparation of compound 34

The captioned compound was prepared as a colorless oil (yield: 42.2 mg) using the compound obtained in (1) (62.1 mg, 0.130 mmole), in the same manner as described in Example 30-(2).

5 IR(neat, cm^{-1}): 2944, 1647, 1605, 1584, 1497, 1458, 1344, 1266, 1122, 1083, 1032

High Resolution FAB-MS (m/z , $(\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_6+\text{H})^+$):

Calcd.: 535.2808

Found : 535.2831

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

10 2.23+2.27(6H, s \times 2), 2.68-2.80(1H, m), 2.80-3.00(1H, m), 2.75(1H, d, $J=14.5\text{Hz}$), 2.78(1H, dd, $J=10.5\text{Hz}$, 13.4Hz), 3.09(1H, dd, $J=2.6\text{Hz}$, 13.4Hz), 3.20-3.40(1H, m), 3.40(1H, d, $J=14.5\text{Hz}$), 3.46+4.07(2H, s \times 2), 3.65+ 3.69 (3H, s \times 2), 3.86+3.88(3H, s \times 2), 3.86+3.93(3H, s \times 2), 4.47+5.95(1H, dd \times 2, $J=2.6\text{Hz}$, 10.5Hz, $J=4.6\text{Hz}$, 8.1Hz), 4.65-4.76(1H, m), 5.06+5.09(1H, d \times 2, $J=11.2\text{Hz}$, $J=10.9\text{Hz}$), 5.19+5.39(1H, d \times 2, $J=11.2\text{Hz}$, $J=10.9\text{Hz}$), 6.40-6.52 (3H, m), 6.70+6.71(1H, dd \times 2, $J=1.9\text{Hz}$, 8.1Hz, $J=1.9\text{Hz}$, 8.1Hz), 7.05+7.07(1H, t \times 2, $J=7.8\text{Hz}$, $J=7.8\text{Hz}$), 7.30-7.50(4H, m)

15 Compounds 35~37 (Examples 35~37) were prepared by the condensation of the compound obtained in Example 34-(1) with the corresponding carboxylic acids, 3-hydroxypropionic acid, methoxyacetic acid, N-acetyl-sarcosine, using dimethylformamide, dichloromethane, dimethylformamide as solvents, in the same manner as described in Example 30-(2).

20

EXAMPLE 35

Compound 35

25 appearance: pale yellow oil

IR(neat, cm^{-1}): 1638, 1605, 1497, 1458, 1437, 1266, 1122, 1092, 1032

High Resolution FAB-MS(m/z , $(\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_6+\text{H})^+$):

Calcd.: 549.2965

Found : 549.2976

30 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

2.22+2.30(6H, s \times 2), 2.60-2.94(3H, m), 3.06-3.26(2H, m), 3.30-3.95(4H, m), 3.43(2H, s), 3.66+3.70(3H, s \times 2), 3.85+3.88(3H, s \times 2), 3.86+3.93(3H, s \times 2), 4.70-4.82+6.05(2H, m+dd, $J=3.4\text{Hz}$, 8.0Hz), 5.08+5.11(1H, d \times 2, $J=11.2\text{Hz}$, $J=11.2\text{Hz}$), 5.38+5.39(1H, d \times 2, $J=11.2\text{Hz}$, $J=11.2\text{Hz}$), 6.40-6.55(3H, m), 6.69+6.71(1H, dd \times 2, $J=2.0\text{Hz}$, 7.7Hz, $J=2.0\text{Hz}$, 7.7Hz), 7.05+7.07(1H, t \times 2, $J=7.7\text{Hz}$, $J=7.7\text{Hz}$), 7.25-7.50(4H, m)

35

EXAMPLE 36

Compound 36

40 appearance: colorless oil

IR(neat, cm^{-1}): 2944, 1656, 1605, 1497, 1458, 1440, 1266, 1122, 1089

High Resolution FAB-MS(m/z , $(\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_6+\text{H})^+$):

Calcd.: 549.2965

Found : 549.2979

45 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

2.25+2.29(6H, s \times 2), 2.50-2.65+2.65-2.77(1H, m \times 2), 2.80(1H, dd, $J=10.6\text{Hz}$, 13.6Hz), 2.85(1H, d, $J=14.3\text{Hz}$), 2.77-2.96(1H, m), 3.01+3.20(3H, s \times 2), 3.10(1H, dd, $J=2.6\text{Hz}$, 13.6Hz), 3.15-3.30(1H, m), 3.36(1H, d, $J=14.3\text{Hz}$), 3.47+3.49(2H, s \times 2), 3.66+3.68(3H, s \times 2), 3.85+3.88(3H, s \times 2), 3.86+3.93(3H, s \times 2), 4.70-4.82 (1H, m), 4.80+6.05(1H, dd \times 2, $J=2.6\text{Hz}$, 10.6Hz, $J=3.5\text{Hz}$, 8.9Hz), 5.05+5.08(1H, d \times 2, $J=11.0\text{Hz}$, $J=11.0\text{Hz}$), 5.20+5.38(1H, d \times 2, $J=11.0\text{Hz}$, $J=11.0\text{Hz}$), 6.41+6.46(1H, s \times 2), 6.45-6.58(2H, m), 6.66+6.71(1H, dd \times 2, $J=1.8\text{Hz}$, 7.8Hz, $J=1.8\text{Hz}$, 7.8Hz), 7.05+7.08(1H, t \times 2, $J=7.8\text{Hz}$, $J=7.8\text{Hz}$), 7.31-7.55(4H, m)

50

EXAMPLE 37

55 Compound 37

appearance: colorless oil

IR(neat, cm^{-1}): 1662, 1605, 1497, 1458, 1437, 1269, 1122, 1089, 1032

High Resolution FAB-MS(m/z , ($C_{34}H_{43}N_3O_8+H$)⁺):

Calcd.: 590.3230

Found : 590.3190

¹H-NMR(300MHz, CDCl₃, δ ppm):

5 1.47+2.02+2.09(3H,s \times 3), 2.09(1H,d,J=16.1Hz), 2.20+2.25+2.29(6H,s \times 3), 2.47+2.48+2.79(3H,s \times 3),
2.60-2.97(2H,m), 3.05-3.30(2H,m), 3.38-3.75(3H,m), 3.66+3.70+3.73(3H,s \times 3), 3.84+3.88+3.89(3H,s \times 3), 3.85+
3.92+3.94(3H,s \times 3), 4.28+4.37(1H,d \times 2, J=16.1Hz, J=16.1Hz), 4.50-4.60+4.70-4.82+6.03(2H, m \times 2+dd, J=3.5Hz,
7.6Hz), 5.06+5.14+5.26(1H,d \times 3, J=11.1Hz, J=10.8Hz, J=11.4Hz), 5.15+5.38+5.40(1H,d \times 3, J=11.1Hz, J=10.8Hz,
10 J=11.4Hz), 6.40-6.60(3H,m), 6.63-6.75(1H,m), 7.05+7.06+7.12(1H,t \times 3, J=8.0Hz, J=8.0Hz, J=8.0Hz), 7.27-7.52
(4H,m)

EXAMPLE 38

Preparation of Compound 38

15 The compound obtained in Example 34-(1) (57.8 mg, 0.121 mmole) was dissolved in dichloromethane (1 ml), and triethylamine (26 μ l, 0.187 mmole) and methane-sulfonyl chloride (15 μ l, 0.194 mmole) were added under an argon atmosphere at 0°C, and the mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate, washed successively with a saturated aqueous sodium hydrogencarbonate solution, brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform: methanol=15:1) to give the captioned compound (50.6 mg) as a colorless oil.

IR(neat, cm⁻¹): 1602, 1584, 1497, 1461, 1320, 1263, 1146, 1122, 1068, 1029

High Resolution FAB-MS(m/z , ($C_{30}H_{38}N_2O_8S+H$)⁺):

25 Calcd.: 555.2529

Found : 555.2533

¹H-NMR(300MHz, CDCl₃, δ ppm):

2.05(3H,s), 2.26(6H,s), 2.61(1H,ddd, J=1.6Hz, 4.2Hz, 16.8Hz), 2.71(1H,dd, J=10.7Hz, 13.9Hz), 3.00(1H,ddd, J=6.4Hz, 11.7Hz, 16.8Hz), 3.19(1H,dd, J=3.7Hz, 13.9Hz), 3.38-3.48(1H,m), 3.49(2H,s), 3.68(3H,s), 3.80-4.00(1H, m),
30 3.86(3H,s), 3.90(3H,s), 5.08(1H,d, J=11.0Hz), 5.13(1H,dd, J=3.7Hz, 10.7Hz), 5.31(1H,d, J=11.0Hz), 6.43(1H, s),
6.52(1H,d, J=7.8Hz), 6.55(1H, d, J=2.0Hz), 6.70(1H,dd, J=2.0Hz, 7.8Hz), 7.08(1H,t, J=7.8Hz), 7.32-7.44(2H,m),
7.46-7.51(2H,m)

EXAMPLE 39

Preparation of Compound 39

35 The compound obtained in Example 34-(1) (57.5 mg, 0.121 mmole) was dissolved in chloroform (1 ml), and acetic anhydride (22 μ l, 0.233 mmole) was added under an argon atmosphere at 0°C, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed successively with a saturated aqueous sodium hydrogencarbonate solution, brine, dried over MgSO₄. The solvent was evaporated, and the residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform: methanol=10:1) to give the captioned compound (57.4 mg) as a colorless oil.

IR(neat, cm⁻¹): 1647, 1605, 1497, 1458, 1428, 1266, 1122, 1101, 1029

45 High Resolution FAB-MS(m/z , ($C_{31}H_{38}N_2O_5+H$)⁺):

Calcd.: 519.2859

Found : 519.2835

¹H-NMR(300MHz, CDCl₃, δ ppm):

1.22+2.02(3H,s \times 2), 2.22+2.31(6H,s \times 2), 2.40-2.60+ 2.60-2.74(1H,m \times 2), 2.79(1H,dd, J=10.5Hz, 13.4Hz),
50 2.75-2.95(1H,m), 3.11(1H,dd, J=2.6Hz, 13.4Hz), 3.07-3.26(1H,m), 3.43(2H,s), 3.65+3.69(3H,s \times 2), 3.85+3.88(3H,
s \times 2), 3.85+3.93(3H,s \times 2), 4.70-4.80 (1H,m), 4.80+6.07(1H,dd \times 2, J=2.6Hz, 10.5Hz, J=4.6Hz, 8.7Hz), 5.02+
5.12(1H,d \times 2, J=10.9Hz, J=10.9Hz), 5.17+5.38(1H,d \times 2, J=10.9Hz, J=10.9Hz), 6.41+6.46(1H,s \times 2), 6.45-
6.55(2H,m), 6.68+6.71(1H, dd \times 2, J=2.1Hz, 7.8Hz, J=2.1Hz, 7.8Hz), 7.04+7.07(1H, t \times 2, J=7.8Hz, J=7.8Hz), 7.28-
7.50(4H,m)

55

EXAMPLE 40

Preparation of Compound 40

- 5 The compound obtained in Example 30-(1) (54.7 mg, 0.115 mmole) was dissolved in tetrahydrofuran (1.5 ml), and methyl isocyanate (12 μ l, 0.203 mmole) was added under an argon atmosphere at 0°C. The mixture was stirred at 0°C for 1 hour and at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform:methanol=10:1) to give the captioned compound (59.2 mg) as pale yellow amorphous.
- 10 IR(KBr, cm⁻¹): 2944, 1632, 1518, 1497, 1467, 1425, 1344, 1248, 1122, 1086, 1032
 High Resolution FAB-MS(m/z, (C₃₁H₃₉N₃O₅+H)⁺):
 Calcd.: 534.2968
 Found : 534.2981
¹H-NMR(300MHz, CDCl₃, δ ppm):
 15 2.23(6H,s), 2.31(3H,d,J=4.6Hz), 2.58(1H,td, J=3.7Hz, 14.9Hz), 2.70(1H,dd,J=10.6Hz, 13.4Hz), 2.78-2.92(1H,m), 3.04-3.13(1H,m), 3.07(1H,dd, J=3.0Hz, 13.4Hz), 3.13-3.30(1H,m), 3.41(1H,d, J=12.8Hz), 3.47(1H,dJ=12.8Hz), 3.75(3H,s), 3.87(3H, s), 3.91(3H,s), 4.29-4.40(1H,m), 4.48-4.60(1H,m), 5.05(1H,d,J=11.3Hz), 5.34(1H,d,J=11.3Hz), 6.44(1H, s), 6.69(2H,d,J=8.8Hz), 6.78(2H,d,J=8.8Hz), 7.30-7.45(4H,m)

20 EXAMPLE 41

Preparation of Compound 41

- 25 The captioned compound was prepared as pale yellow crystals (yield: 57.8mg) using the compound obtained in Example 30-(1) (52.0 mg, 0.109 mmole) and methyl isothiocyanate (8.7 mg, 0.12 mmole), in the same manner described in Example 40.
- IR(KBr, cm⁻¹): 3406, 2938, 2830, 2776, 1611, 1584, 1518, 1497, 1467, 1374, 1344, 1305, 1245, 1179, 1122, 1086, 1032, 960, 843, 819, 792
 High Resolution FAB-MS(m/z, (C₃₁H₃₉N₃O₄S+H)⁺):
 30 Calcd.: 550.2739
 Found : 550.2742
¹H-NMR(300MHz, CDCl₃, δ ppm):
 2.26(6H,s), 2.65(3H,d,J=4.1Hz), 2.81(1H,dd, J=10.0Hz, 13.4Hz), 2.95-3.10(1H,m), 3.17(1H,dd, J=2.9Hz, 13.4Hz), 3.40-3.58(3H,m), 3.74(3H,s), 3.87 (3H,s), 3.90(3H,s), 4.22-4.35(1H,m), 4.86-5.17(2H, m), 5.02(1H,d,J=11.1Hz), 5.31(1H,d,J=11.1Hz), 6.45 (1H,s), 6.68(2H,d,J=8.6Hz), 6.75(2H,d,J=8.6Hz), 7.30-7.50(4H,m)
- 35

EXAMPLE 42

Preparation of Compound 42

- 40 2-(tert-Butyldimethylsiloxy)ethylamine (20.0 mg, 0.114 mmole) was dissolved in tetrahydrofuran (1 ml), and 1,1'-carbonyldiimidazole (18.5 mg, 0.114 mmole) was added at room temperature under an argon atmosphere, and the mixture was stirred for 30 minutes. To the mixture was added a solution of the compound obtained in Example 30-(1) (30.0 mg, 0.0629 mmole) in tetrahydrofuran (1 ml), and the mixture was stirred at room temperature for 6 hours. The reaction mixture was diluted with ethyl acetate, washed successively with water and brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by dry column flash chromatography (silica gel/chloroform: methanol=20:1) to give a pale yellow oil (32.5 mg). This product was dissolved in tetrahydrofuran (2 ml), and a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (60 μ l) was added at 0°C, and the mixture was stirred for 2 hours. The reaction mixture was diluted with ethyl acetate, washed successively with water and brine, and dried over MgSO₄. The solvent was evaporated, and the residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform:methanol=8:1) to give the captioned compound (20.9 mg) as a colorless oil.
- 50 IR(neat, cm⁻¹): 3382, 2944, 2782, 1614, 1518, 1467, 1248, 1122, 1086, 1032, 753
 High Resolution FAB-MS (m/z, (C₃₂H₄₁N₃O₈+H)⁺):
 55 Calcd.: 564.3074
 Found : 564.3055
¹H-NMR(300MHz, CDCl₃, δ ppm):
 2.24(6H,s), 2.55-2.67(1H,m), 2.72(1H,dd,J=10.4Hz, 13.7Hz), 2.74-

2.96(3H,m), 3.08(1H,dd,J=2.7Hz,13.7Hz)3.23(1H,ddd,J=4.5Hz,11.5Hz,13.3Hz),3.33 (2H,t,J=5.1Hz),3.44(1H,d,J=12.7Hz),3.53(1H,d, J=12.7Hz),3.68-3.74(2H,m),3.75(3H,s),3.87(3H,s), 3.94(3H,s),4.30-4.42(1H,m),4.46-4.58(1H,m), 5.00 (1H,d,J=10.9Hz),5.36(1H,d,J=10.9Hz),6.46(1H,s), 6.70(2H,d,J=8.5Hz),6.80(2H,d,J=8.5Hz),7.31-7.55 (4H,m)

5 EXAMPLE 43

Preparation of Compound 43

To a solution of the compound obtained in Example 30-(1) (50.3 mg, 0.106 mmole) in dichloromethane (2 ml), were added 4-dimethylaminopyridine (8.0 mg, 0.065 mmole) and dimethylcarbamoyl chloride (15 μ l, 0.163 mmole) at 0°C under an argon atmosphere, and the mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by dry column flash chromatography (silica gel/chloroform:methanol=30:1) to give the captioned compound (47.8 mg) as a pale yellow oil.

15 IR(neat, cm⁻¹): 1644,1515,1497,1461,1248,1122,1095, 1032

High Resolution FAB-MS(m/z, (C₃₂H₄₁N₃O₅+H)⁺):

Calcd.: 548.3124

Found : 548.3094

¹H-NMR(300MHz, CDCl₃, δ ppm):

20 2.25(6H,s),2.41(6H,s),2.58-2.69(1H,m),2.80(1H, dd,J=10.7Hz,14.2Hz),2.80-3.00(1H,m),3.06(1H,dd, J=3.2Hz,14.2Hz),3.48-3.52(1H,m),3.47(2H,s),3.75-3.88(1H,m),3.75(3H,s),3.85(3H,s),3.90(3H,s),5.06 (1H,d,J=10.9Hz),5.33(1H,d,J=10.9Hz),5.16(1H,dd, J=3.2Hz,10.7Hz),6.43(1H,s),6.68(2H,d,J=8.6Hz), 6.89(2H,d,J=8.6Hz), 7.30-7.53(4H,m)

25 EXAMPLE 44

Preparation of Compound 44

The compound obtained in Example 30-(1) (29.8 mg, 0.0625 mmole) was dissolved in acetonitrile (2 ml), and chlorosulfonyl isocyanate (12 μ l, 0.139 mmole) was added under nitrogen at 0°C, and the mixture was stirred at room temperature for 3 hours. To the mixture was added water (0.2 ml), and the reaction mixture was stirred for 1 hour. The resulting mixture was diluted with ethyl acetate, washed successively with a saturated aqueous sodium hydrogencarbonate solution and brine, and dried over MgSO₄. The organic layer was concentrated under reduced pressure and the residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform:methanol=7:1) to give the captioned compound (5.5 mg) as a pale yellow oil.

IR(neat, cm⁻¹): 1584,1515,1497,1467,1344,1248,1122, 1032,753

High Resolution FAB-MS(m/z, (C₃₀H₃₇N₃O₅+H)⁺):

Calcd.: 520.2812

Found : 520.2787

¹H-NMR(300MHz, CDCl₃, δ ppm):

40 2.32+2.61(6H,s \times 2),2.40-3.35(3H,m),2.72(1H,dd, J=10.0Hz,13.7Hz),3.09(1H,dd,J=3.0Hz,13.7Hz),3.59 (2H,s),3.75+3.84(3H,s \times 2),3.86+3.97(3H,s \times 2), 3.91+3.95(3H,s \times 2),4.25-4.45(1H,m),4.60-4.72(1H, m), 5.03+5.06(1H,d \times 2,J=11.2Hz,J=11.2Hz),5.36+ 5.45(1H,d \times 2,J=11.2Hz,J=11.2Hz),6.38+6.44(1H,s \times 2),6.67 (2H,d,J=g.8Hz),6.77(2H,d,J=8.gHz),7.35-7.-60(4H,m)

45 Compounds 45 and 46 (Examples 45 and 46) were prepared using compound 26 obtained in Example 26, in the same manner as described in Example 30-(1) and Examples 40,30-(2).

EXAMPLE 45

Compound 45

appearance: pale yellow amorphous

IR(KBR, cm⁻¹): 1638,1605,1539,1497,1461,1260,1122

55 High Resolution FAB-MS(m/z, (C₃₁H₃₉N₃O₅+H)⁺):

Calcd.: 534.2968

Found : 534.2996

¹H-NMR(300MHz, CDCl₃, δ ppm):

2.18(6H,s),2.32(3H,d,J=4.6Hz),2.59(1H,td, J=3.3Hz,16.2Hz),2.76(1H,dd,J=10.0Hz,13.3Hz),2.87 (1H,td, J=5.3Hz,16.2Hz),3.10(1H,dd,J=3.0Hz, 13.3Hz),3.23(1H,ddd,J=3.3Hz,5.3Hz,13.2Hz),3.14-3.19(1H,m),3.43(1H, d,J=12.9Hz),3.56(1H,d, J=12.9Hz),3.65(3H,s),3.87(3H,s),3.90(3H,s),4.24-4.35(1H,m),4.59-4.69(1H,m),5.17(1H, d,J=11.7Hz), 5.55(1H,d,J=11.7Hz),6.36(1H,d,J=7.8Hz),6.45(1H, s),6.47(1H,d,J=2.0Hz),6.68(1H,dd,J=2.0Hz, 7.8Hz), 7.04(1H,t,J=7.8Hz),7.30-7.42(3H,m),7.55-7.62(1H, m)

EXAMPLE 46

Compound 46

10

appearance: colorless oil

IR(neat, cm^{-1}): 1650,1605,1497,1458,1266,1122,1083, 756

High Resolution FAB-MS(m/z , $(\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_6+\text{H})^+$):

Calcd.: 535.2808

15

Found : 535.2803

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δppm):

2.21+2.24(6H,s \times 2),2.70-3.02(3H,m),2.77(1H,d, J=14.8Hz),3.09(1H,dd,J=3.0Hz,13.7Hz),3.17-3.37 (1H, m),3.35-3.60(2H,m),3.52(1H,d,J=14.8Hz),3.64 (3H,s),3.84+3.88(3H,s \times 2),3.89+3.92(3H,s \times 2), 4.45+5.90(1H, dd \times 2,J=3.0Hz,10.5Hz,J=4.8Hz, 7.2Hz),4.65-4.76(1H,m),5.14+5.21(1H,d \times 2, J=11.7Hz,J=11.7Hz),5.39+ 20 5.62(1H,d \times 2,J=11.7Hz, J=11.7Hz),6.34(1H,d,J=7.6Hz),6.41(1H,d,J=2.0Hz), 6.47(1H,s),6.69+6.70(1H,dd \times 2,J=2.0Hz,7.6Hz, J=2.0Hz,7.6Hz),7.03+7.05(1H,t \times 2,J=7.6Hz, J=7.6Hz),7.30-7.66(4H,m)

EXAMPLE 47

25 (1) Preparation of 2-chloroacetyl-6,7-dimethoxy-8-(3-dimethylaminomethylbenzyloxy)-1-(4-methoxybenzyl)- 1,2,3, 4-tetrahydroisoquinoline

The compound obtained in Example 30-(1) (210 mg, 0.440 mmole) was dissolved in dichloromethane (3 ml), and a solution of chloroacetic acid (92 mg, 0.538 mmole) in dichloromethane (0.5 ml) was added at room temperature under an argon atmosphere, and the mixture was stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate, washed successively with a saturated aqueous sodium hydrogencarbonate solution and brine. The organic layer was dried over MgSO_4 and concentrated under reduced pressure to give the desired compound (206 mg) as a pale yellow oil.

35

FAB-MS (m/z , $(\text{C}_{31}\text{H}_{37}\text{N}_2\text{O}_5\text{Cl}+\text{H})^+$): 553

(2) Preparation of compound 47

The compound obtained in (1) (100 mg, 0.187 mmole) was dissolved in dimethylformamide, and thioacetic S-acid (20 μl , 0.280 mmole) was added at room temperature under an argon atmosphere, and the mixture was stirred for 6 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform:methanol=10:1) to give the captioned compound (50.1 mg) as a colorless oil.

40

IR(neat, cm^{-1}): 2944,2820,1695,1647,1515,1431,1248, 1122,1089,1032,960,835

High Resolution FAB-MS(m/z , $(\text{C}_{33}\text{H}_{40}\text{N}_2\text{O}_6\text{S}+\text{H})^+$):

45

Calcd.: 593.2686

Found : 593.2710

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δppm):

2.24+2.26(6H,s \times 2),2.30+2.35(3H,s \times 2),2.34(1H,d, J=15.4Hz),2.65-2.97(2H,m),2.74(1H,dd,J=10.6Hz, 13.6Hz),3.12(1H,dd,J=2.2Hz,13.6Hz),3.13-3.27(1H, m),3.28(1H,d,J=15.4Hz),3.49+3.56(2H,s \times 2),3.75+ 3.76 (3H,s \times 2),3.86+3.88(3H,s \times 2),3.94(3H,s), 4.70-4.80(1H,m),4.91+5.95(1H,dd \times 2,J=2.2Hz, 10.6Hz,J=4.7Hz, 50 8.6Hz),5.02+5.09(1H,d \times 2, J=10.9Hz,J=10.7Hz),5.16+5.43(1H,d \times 2,J=10.9Hz, J=10.7Hz),6.41+6.46(1H,s \times 2),6.63-6.85(4H,m), 7.34-7.57(4H,m)

EXAMPLE 48

55

Preparation of Compound 48

The compound obtained in Example 47-(1) (43.0 mg, 0.077 mmole) was dissolved in dimethyl sulfoxide

(0.5 ml), and a 15% aqueous sodium methyl sulfide solution (55 μ l) was added at room temperature under an argon atmosphere, and the mixture was stirred overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform:methanol=10:1) to give the captioned compound (18.2 mg) as a pale yellow oil.

High Resolution FAB-MS(m/z , ($\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_5\text{S}+\text{H}$)⁺):

Calcd.: 565.2736

Found : 565.2746

¹H-NMR(300MHz, CDCl_3 , δ ppm):

1.92(3H,s), 2.29+2.33(6H,s \times 2), 2.61(2H,s), 2.73 (1H,dd,J=10.3Hz,13.4Hz), 2.80-2.95(1H,m), 3.09(1H,dd,J=2.8Hz,13.6Hz), 3.12-3.24(1H,m), 3.53(2H,s), 3.55-3.68(1H,m), 3.73+3.75(3H,s \times 2), 3.87+3.88(3H,s \times 2), 3.93+3.95(3H,s \times 2), 4.90+5.95-6.02(1H,dd+m, J=2.0Hz,10.3Hz), 4.72-4.81(1H,m), 4.98+5.06(1H,d \times 2, J=10.8Hz, J=10.8Hz), 5.22+5.45(1H,d \times 2, J=10.8Hz, J=10.8Hz), 6.42+6.47(1H,s \times 2), 6.63-6.73+6.83-6.90 (4H,m \times 2), 7.38-7.55(4H,m)

EXAMPLE 49

Preparation of Compound 49

The compound obtained in Example 47-(1) (70.5 mg, 0.127 mmole) was dissolved in ethanol, and morpholine (350 μ l, 4.01 mmole) was added under an argon atmosphere, and the mixture was heated under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure, and ethyl acetate was added to the residue. The mixture was washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform:methanol=10:1) to give the captioned compound (67.2 mg) as a colorless oil,

IR(neat, cm^{-1}): 1644, 1515, 1458, 1344, 1248, 1119, 1092, 1029

High Resolution FAB-MS(m/z , ($\text{C}_{35}\text{H}_{45}\text{N}_3\text{O}_6+\text{H}$)⁺):

Calcd.: 604.3387

Found : 604.3367

¹H-NMR(300MHz, CDCl_3 , δ ppm):

2.05(1H,d,J=14.4Hz), 2.14(4H,t,J=4.6Hz), 2.26+2.31 (6H,s \times 2), 2.44(1H,d,J=14.4Hz), 2.60-3.00(3H,m), 3.07(1H,dd,J=2.5Hz,13.8Hz), 3.14-3.30(1H,m), 3.45-3.65(6H,m), 3.72+3.75(3H,s \times 2), 3.86+3.88(3H,s \times 2), 3.88+3.91(3H,s \times 2), 4.76+6.06(1H,dd \times 2, J=5.9Hz,11.9Hz, J=3.5Hz,10.0Hz), 5.06+5.20(1H,d \times 2, J=10.7Hz, J=11.0Hz), 5.24+5.35(1H,d \times 2, J=10.7Hz, J=11.0Hz), 5.10-5.20(1H,m), 6.42+6.46(1H,s \times 2), 6.66+6.69(2H,d \times 2, J=8.8Hz, J=8.8Hz), 6.76+6.87(2H,d \times 2, J=8.8Hz, J=8.8Hz), 7.36-7.57(4H,m)

Compounds 50 and 51 (Examples 50 and 51) were prepared using the compound obtained in Example 34-(1), in the same manner as described in Examples 48 and 47. Compound 52 (Example 52) was prepared using intermediate 5 obtained in Referential Example 5, in the same manners as described in Examples 26, 30-(1) and 47. Compound 53 (Example 53) was prepared using compound 20 obtained in Example 20, in the same manners as described in Examples 30-(1) and 47.

EXAMPLE 50

Compound 50

appearance: pale yellow oil

IR(neat, cm^{-1}): 1644, 1605, 1497, 1458, 1437, 1266, 1122, 1089

High Resolution FAB-MS(m/z , ($\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_5\text{S}+\text{H}$)⁺):

Calcd.: 565.2736

Found : 565.2765

¹H-NMR(300MHz, CDCl_3 , δ ppm):

1.91(3H,s), 2.26+2.28(6H,s \times 2), 2.33(1H,d, J=14.1Hz), 2.41(1H,d,J=14.1Hz), 2.55-2.80(1H,m), 2.79(1H,dd,J=10.4Hz,13.4Hz), 2.80-2.97(1H,m), 3.15 (1H,dd,J=2.5Hz,13.4Hz), 3.15-3.29(1H,m), 3.50(2H, s), 3.65+3.66(3H,s \times 2), 3.86+3.88(3H,s \times 2), 3.87+ 3.94(3H,s \times 2), 4.71-4.82(1H,m), 4.99+6.06(1H,dd \times 2, J=2.5Hz,10.4Hz, J=4.1Hz,8.8Hz), 5.03+5.08(1H,d \times 2, J=10.8Hz, J=10.8Hz), 5.21+5.43(1H,d \times 2, J=10.8Hz, J=10.8Hz), 6.48-6.60(3H,m), 6.67+6.70(1H,dd \times 2, J=2.1Hz,7.5Hz, J=2.1Hz,7.5Hz), 7.04+7.05(1H,t \times 2, J=7.5Hz, J=7.5Hz), 7.35-7.55(4H,m)

EXAMPLE 51

Compound 51

- 5 appearance: brown oil
 IR(neat, cm^{-1}): 1698, 1650, 1605, 1497, 1458, 1437, 1269, 1122, 1089, 1032
 High Resolution FAB-MS(m/z , $(\text{C}_{33}\text{H}_{40}\text{N}_2\text{O}_6\text{S}+\text{H})^+$):
 Calcd.: 593.2686
 Found : 593.2690
- 10 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):
 2.24+2.29(6H, s \times 2), 2.24+2.35(3H, s \times 2), 2.44(1H, d, $J=15.4\text{Hz}$), 2.65-2.77(1H, m), 2.80(1H, dd, $J=10.7\text{Hz}$,
 13.4Hz), 2.75-2.95(1H, m), 3.13-3.30(2H, m), 3.28(1H, d, $J=15.4\text{Hz}$), 3.47+3.54(2H, s \times 2), 3.65+3.68(3H, s \times 2), 3.85+
 3.88(3H, s \times 2), 3.86+3.93(3H, s \times 2), 4.69-4.79(1H, m), 4.95-5.03+6.01(1H, m+dd, $J=5.8\text{Hz}$, 8.1Hz), 5.01+5.13
 (1H, d \times 2, $J=10.9\text{Hz}$, $J=10.9\text{Hz}$), 5.14+5.39(1H, d \times 2, $J=10.9\text{Hz}$, $J=10.9\text{Hz}$), 6.40-6.55 (3H, m), 6.68+6.71(1H, dd \times
 15 2, $J=2.3\text{Hz}$, 7.8Hz, $J=2.3\text{Hz}$, 7.8Hz), 7.04+7.08(1H, t \times 2, $J=7.8\text{Hz}$, $J=7.8\text{Hz}$), 7.30-7.50(4H, m)

EXAMPLE 52

Compound 52

- 20 appearance: colorless oil
 IR(neat, cm^{-1}): 2944, 2836, 2770, 1695, 1647, 1506, 1464,
 1344, 1227, 1122, 1089, 966, 753
 High Resolution FAB-MS (m/z , $(\text{C}_{34}\text{H}_{42}\text{N}_2\text{O}_4\text{S}+\text{H})^+$):
 25 Calcd.: 623.2791
 Found : 623.2783
- $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):
 2.21+2.26(6H, s \times 2), 2.25+2.33(3H, s \times 2), 2.76-3.21 (4H, m), 3.36-3.85(5H, m), 3.53+3.55(3H, s \times 2), 3.57+
 3.59(3H, s \times 2), 3.80+3.85(3H, s \times 2), 3.86+3.88(3H, s \times 2), 4.47(1H, ddd, $J=3.4\text{Hz}$, 5.9Hz, 13.0Hz), 5.11+5.25 (1H, d
 30 \times 2, $J=11.8\text{Hz}$, $J=11.9\text{Hz}$), 5.19+6.06(1H, dd \times 2, $J=3.0\text{Hz}$, 8.7Hz, $J=5.1\text{Hz}$, 9.0Hz), 5.32+5.46(1H, d \times 2, $J=11.8\text{Hz}$,
 $J=11.9\text{Hz}$), 6.33-6.52(1H, m), 6.45+6.50(1H, s \times 2), 6.60-6.70(2H, m), 7.22-7.49(3H, m), 7.63-7.74 (1H, m)

EXAMPLE 53

Compound 53

- 35 appearance: yellow oil
 IR(neat, cm^{-1}): 2920, 2812, 1695, 1647, 1482, 1440, 1263, 1209, 1116, 1041, 966, 753
 High Resolution FAB-MS (m/z , $(\text{C}_{34}\text{H}_{38}\text{N}_2\text{O}_7\text{S}+\text{H})^+$):
 40 Calcd.: 619.2478
 Found : 619.2474
- $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):
 2.23+2.34(3H, s \times 2), 2.33-2.49(4H, m), 2.52(1H, d, $J=15.4\text{Hz}$), 2.61-2.95(3H, m), 3.08-3.27(2H, m), 3.38 (1H, d,
 $J=15.4\text{Hz}$), 3.50(2H, s), 3.57-3.73(4H, m), 3.66+3.75(3H, s \times 2), 4.63-4.74(1H, m), 5.03+5.95-6.05(1H, dd+m, $J=2.2\text{Hz}$,
 45 10.3Hz), 5.22+5.35(1H, s+d, $J=11.0\text{Hz}$), 5.22+5.44(1H, s+d, $J=11.0\text{Hz}$), 5.92+5.97 (1H, d+s, $J=7.8\text{Hz}$), 5.93+5.97
 (1H, d+s, $J=7.8\text{Hz}$), 6.31+ 6.37(1H, s \times 2), 6.45-6.56(2H, m), 6.64-6.77(1H, m),
 7.00-7.12(1H, m), 7.26-7.52(4H, m)

EXAMPLE 54

- 50 (1) Preparation of 2-chloroacetyl-6,7-dimethoxy-8-(2-dimethylaminomethylbenzyloxy)-1-(3-methoxybenzyl)-
 1,2,3, 4-tetrahydroisoquinoline

The desired compound was prepared as a pale yellow oil (yield: 83 mg) using compound 26 obtained in
 55 Example 26 (104 mg), in the same manner as described in Example 30-(1) and Example 47-(1).
 FAB-MS(m/z , $(\text{C}_{31}\text{H}_{37}\text{N}_2\text{O}_5\text{Cl}+\text{H})^+$): 553

(2) Preparation of compound 54

To a suspension of sodium hydride (6.5 mg, 0.162 mmole, 60%) in dimethylformamide (1 ml) was added 2-pyrrolidone (12 μ l, 0.158 mmole), and the mixture was stirred at 70°C under an argon atmosphere for 10 minutes. The mixture was cooled to room temperature. To the mixture was added dropwise a solution of the compound obtained in (1) (83.0 mg, 0.150 mmole) in dimethylformamide (1 ml), and the reaction mixture was stirred at room temperature for 1 hour. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform:methanol=10:1), and was triturated in ether to give the captioned compound (65.4 mg) as a colorless powder.

IR(KBR, cm^{-1}): 2944, 1692, 1659, 1605, 1497, 1458, 1269, 1122

High Resolution FAB-MS(m/z , $(\text{C}_{35}\text{H}_{43}\text{N}_3\text{O}_6+\text{H})^+$):

Calcd.: 602.3230

Found : 602.3230

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

1.80-2.05(2H,m), 2.13(1H,d,J=16.3Hz), 2.22(6H,s), 2.20-2.40(2H,m), 2.55(1H,dt,J=5.4Hz,8.4Hz), 2.60-3.00(2H,m), 2.81(1H,dd,J=10.7Hz,13.2Hz), 3.13(1H,dd,J=2.6Hz,13.2Hz), 3.15-3.30(2H,m), 3.45-3.60(2H,m), 3.62+3.65(3H,s \times 2), 3.84+3.89(3H,s \times 2), 3.87+3.91(3H,s \times 2), 4.02(1H,d,J=16.3Hz), 4.70-4.78+5.98(1H,m+dd,J=4.8Hz,14.9Hz), 4.72-4.81(1H,m), 5.12+5.31(1H,d \times 2,J=11.9Hz,J=11.9Hz), 5.39+5.59(1H,d \times 2,J=11.9Hz), J=11.9Hz), 6.32(1H,d,J=7.6Hz), 6.35-6.55(1H,m), 6.46(1H,s), 6.65+6.71(1H,dd \times 2,J=1.8Hz,7.8Hz,J=1.8Hz,7.8Hz), 7.04(1H,t,J=7.8Hz), 7.25-7.45(3H,m), 7.59-7.70(1H,m)

EXAMPLE 55

Preparation of Compound 55

To a suspension of 6,7-dimethoxy-1-(4-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (50.3 mg, 0.153 mmole) in dichloromethane (1.5 ml) were added triethylamine (25 μ l, 0.18 mmole) and methyl chloroformate (14 μ l, 0.18 mmole) at 0°C, and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with dichloromethane, washed successively with 10% aqueous citric acid and brine. The organic layer was dried over MgSO_4 and concentrated under reduced pressure to give a yellow oil. Using this product, the captioned compound was prepared as a pale yellow oil (22.5 mg) in the same manner as described in Example 1-(1).

IR(neat, cm^{-1}): 2944, 2770, 1704, 1608, 1518, 1458, 1368, 1248, 1119, 1032, 840, 792, 759

High Resolution FAB-MS (m/z , $(\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_6+\text{H})^+$):

Calcd.: 535.2808

Found : 535.2841

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

2.24(6H,s), 2.40-2.91(2H,m), 2.69(1H,dd,J=10.3Hz, 13.7Hz), 3.06(1H,dd,J=3.2Hz,13.7Hz), 3.22+3.58(3H,s \times 2), 3.28-3.42(1H,m), 3.46(2H,s), 3.74(3H,s), 3.87(3H,s), 3.86+3.90(3H,s \times 2), 4.20(1H,ddd,J=2.7Hz, 6.2Hz,8.7Hz), 5.04(1H,d,J=10.8Hz), 5.18+5.30(1H,d \times 2,J=10.8Hz,J=10.8Hz), 5.24+5.57(1H,dd \times 2, J=3.2Hz,10.3Hz,J=3.2Hz, 10.3Hz), 6.40+6.45(1H,s \times 2), 6.68(2H,d,J=8.8Hz), 6.78+6.84(2H,d \times 2,J=8.8Hz, J=8.8Hz), 7.30-7.50(4H,m)

Compounds 56 and 57 (Examples 56 and 57) were prepared using methanesulfonyl chloride, acetyl chloride in the same manner as described in Example 55.

EXAMPLE 56

Compound 56

appearance: pale yellow oil

High Resolution FAB-MS(m/z , $(\text{C}_{30}\text{H}_{38}\text{N}_2\text{O}_6+\text{H})^+$):

Calcd.: 555.2529

Found : 555.2511

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

2.04(3H,s), 2.25(6H,s), 2.57-2.68(1H,m), 2.65(1H,dd,J=10.9Hz,13.9Hz), 2.94-3.08(1H,m), 3.13(1H,dd,J=3.4Hz,13.9Hz), 3.38-3.45(1H,m), 3.47(2H,s), 3.75(3H,s), 3.84-3.89(1H,m), 3.86(3H,s), 3.91(3H,s), 5.02(1H,dd,J=3.4Hz,10.9Hz), 5.04(1H,d,J=10.9Hz), 5.32(1H,d,J=10.9Hz), 6.43(1H,s), 6.67-6.72(2H,m), 6.79-6.83(2H,m), 7.34-

7.51(4H,m)

EXAMPLE 57

5 Compound 57

appearance: colorless oil

IR(neat, cm^{-1}): 2938,1650,1608,1518,1458,1428,1368, 1364,1248,1122,1098,1029,834,753High Resolution FAB-MS(m/z , $(\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_5+\text{H})^+$):

10 Calcd.: 519.2859

Found : 519.2854

 $^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

1.19(3H,s),2.22+2.25(6H,s \times 2),2.62-2.92(2H,m), 2.73(1H,dd,J=10.7Hz,13.7Hz),3.06(1H,dd,J=2.7Hz,
13.7Hz),3.11-3.28(1H,m),3.42(2H,s),3.74+3.75(3H, s \times 2),3.85+3.88(3H,s \times 2),3.93(3H,s),4.72+5.96-6.05(1H,
15 dd+m,J=2.7Hz,10.7Hz),4.69-4.80(1H,m), 5.03+5.08(1H,d \times 2,J=11.1Hz,J=11.1Hz),5.16+5.40 (1H,d \times 2,J=11.1Hz,
J=11.1Hz),6.40+6.45(1H,s \times 2), 6.65-6.83(4H,m),7.30-7.50(4H,m)

EXAMPLE 58

20 (1) Preparation of 6,7-dimethoxy-1-(4-methoxybenzyl)-2-(N,N-dimethylaminoacetyl)-1,2,3,4-tetrahydroisoquinolin-8-ol

To a suspension of 6,7-dimethoxy-1-(4-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (103 mg, 0.312 mmole) in dichloromethane (2 ml) were added N,N-dimethylglycine hydrochloride (52.2 mg, 0.374 mmole) and
25 HOBt (57.3 mg, 0.374 mmole) at room temperature under nitrogen. Then triethylamine (56.5 μl , 0.405 mmole) and EDCI (71.7 mg, 0.374 mmole) were added to the mixture at 0°C . The reaction mixture was stirred at 0°C for 1.5 hours and at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue. The mixture was extracted with chloroform. The combined extracts were successively washed with a saturated aqueous sodium hydrogencarbonate solution and brine, dried over
30 MgSO_4 , and concentrated under reduced pressure. The residue was recrystallized from methanol to give the desired compound (78.4 mg) as colorless crystals.

m.p.: 185-187 $^\circ\text{C}$ FAB-MS (m/z , $(\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_5+\text{H})^+$): 41535 (2) Preparation of compound 58

The captioned compound was prepared as a colorless oil (yield: 35.6 mg) using the compound obtained in (1) in the same manner as described in Example 1-(1).

IR(neat, cm^{-1}): 2938,2776,1611,1500,1344,1122,103540 High Resolution FAB-MS (m/z , $(\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_5+\text{H})^+$):

Calcd.: 562.3281

Found : 562.3257

 $^1\text{H-NMR}$ (300MHz, $\text{CDCl}_3+\text{D}_2\text{O}$, δ ppm):

1.96+2.08(6H,s \times 2),1.99(1H,d,J=14.4Hz),2.25+2.26 (6H,s \times 2),2.40(1H,d,J=14.4Hz),2.77(1H,dd,
45 J=10.6Hz,13.6Hz),2.60-2.95(2H,m),3.10(1H,dd, J=2.6Hz,13.6Hz),3.06-3.25(1H,m),3.48+3.49(2H,s \times 2),3.72+
3.75(3H,s \times 2),3.86+3.88(3H,s \times 2),3.87+ 3.92(3H,s \times 2),4.67-4.75(1H,m),5.04(1H,d, J=10.9Hz),5.22-5.26
(1H,m),5.36(1H,d,J=10.9Hz), 6.41+6.47(1H,s \times 2),6.66-6.73(2H,m),6.79-6.89(2H, m),7.33-7.49(4H,m)

Compounds 59 and 60 (Examples 59 and 60) were prepared by the reaction of 6,7-dimethoxy-1-(3-methoxy-benzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol with the corresponding chlorides, 3-chloromethyl-N,N-dimethyl-benzylamine hydrochloride, N-(3-chloromethylbenzyl)-N'-methylpiperazine dihydrochloride, in the same
50 manner as described in Example 55.

EXAMPLE 59

55 Compound 59

appearance: pale yellow oil

IR(neat, cm^{-1}): 2944,1704,1605,1497,1455,1341,1251, 1119,1032

High Resolution FAB-MS(m/z, (C₃₁H₃₈N₂O₆+H)⁺):

Calcd.: 535.2808

Found : 535.2834

¹H-NMR(300MHz, CDCl₃, δppm):

2.24(6H,s), 2.40-2.53+2.63(1H,m+td, J=2.9Hz, 14.6Hz), 2.76(1H,dd, J=10.3Hz, 13.5Hz), 2.75-2.92 (1H,m), 3.11(1H,dd, J=3.2Hz, 13.5Hz), 3.24+3.60(3H,s × 2), 3.28-3.45(1H,m), 3.45(2H,s), 3.66+3.67(3H,s × 2), 3.85+3.89(3H,s × 2), 3.87(3H,s), 4.19(1H,ddd, J=2.9Hz, 6.4Hz, 13.2Hz), 5.05+5.07(1H,d × 2, J=11.0Hz, J=11.0Hz), 5.17+5.28(1H,d × 2, J=11.0Hz, J=11.0Hz), 5.30+5.62(1H,dd × 2, J=3.2Hz, 10.3Hz, J=3.2Hz, 10.3Hz), 6.41+6.45(1H,s × 2), 6.45-6.60(2H, m), 6.67(1H,dd, J=1.1Hz, 8.1Hz), 7.06(1H,t, J=8.1Hz), 7.25-7.50(4H,m)

EXAMPLE 60

Compound 60

appearance: colorless oil

IR(neat, cm⁻¹): 2944, 2800, 1704, 1605, 1497, 1458, 1341, 1248, 1164, 1119, 1014

High Resolution FAB-MS (m/z, (C₃₄H₄₃N₃O₆+H)⁺):

Calcd.: 590.3230

Found : 590.3209

¹H-NMR(300MHz, CDCl₃, δppm):

2.28(3H,s), 2.33-2.60(8H,m), 2.50-2.70(1H,m), 2.75 (1H,dd, J=10.1Hz, 13.4Hz), 2.75-2.91(1H,m), 3.10(1H,dd, J=3.6Hz, 13.4Hz), 3.24+3.60(3H,s × 2), 3.25-3.46 (1H,m), 3.53(2H,s), 3.66+3.67(3H,s × 2), 3.85+3.90 (3H,s × 2), 3.87(3H,s), 4.13-4.24(1H,m), 5.04+5.07 (1H,d × 2, J=11.1Hz, J=11.1Hz), 5.15+5.26(1H,d × 2, J=11.1Hz, J=11.1Hz), 5.29+5.61(1H,dd × 2, J=3.6Hz, 10.1Hz, J=4.7Hz, 8.2Hz), 6.42+6.45(1H,s × 2), 6.47-6.59(2H,m), 6.68(1H,d, J=8.2Hz), 7.06(1H,t, J=8.2Hz), 7.30-7.50(4H,m)

EXAMPLE 61

(1) Preparation of 6,7-dimethoxy-1-(3-methoxybenzyl)-2-(N-methylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-8-ol

To a solution of 6,7-dimethoxy-1-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol (350 mg, 1.06 mmole) in dichloromethane (11 ml) was added methyl isocyanate (69 μl, 1.17 mmole) at room temperature under an argon atmosphere, and the reaction mixture was stirred for 3.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel/chloroform:methanol=20:1) to give the desired compound (410 mg) as a colorless powder.

m.p.: 75-80°C

FAB-MS (m/z, (C₂₁H₂₈N₂O₅+H)⁺): 387

(2) Preparation of compound 61

The captioned compound was prepared as a yellow oil (yield: 58.1 mg) using the compound obtained in (1) (57.2 mg, 0.148 mmole) and 2-chloromethylpyridine hydrochloride (32.0 mg, 0.195 mmole) in the same manner as described in Example 1-(1).

IR(neat, cm⁻¹): 3376, 2938, 1635, 1608, 1542, 1497, 1461, 1440, 1374, 1344, 1260, 1194, 1152, 1122, 1086, 1044, 1005, 759

High Resolution FAB-MS (m/z, (C₂₇H₃₁N₃O₅+H)⁺):

Calcd.: 478.2342

Found : 478.2359

¹H-NMR(300MHz, CDCl₃, δ ppm):

2.44(3H,d, J=4.7Hz), 2.56-2.68(1H,m), 2.70-2.92(2H, m), 3.10(1H,dd, J=3.2Hz, 13.4Hz), 3.24-3.36(1H,m), 3.69(3H,s), 3.86(3H,s), 3.90(3H,s), 4.03-4.10(1H, m), 4.29-4.37(1H,m), 5.10-5.18(1H,m), 5.11(1H,d, J=12.0Hz), 5.41(1H,d, J=12.0Hz), 6.46(1H,s), 6.52-6.60(2H,m), 6.68-6.71(1H,m), 7.08(1H,t, J=7.8Hz), 7.25-7.31(1H,m), 7.53(1H, d, J=8.5Hz), 7.76(1H,t, J=8.5Hz), 8.55-8.60(1H,m)

Compounds 62 and 63 (Examples 62 and 63) were prepared using 3-chloromethylpyridine hydrochloride, 4-chloromethylpyridine hydrochloride in the same manner as described in Example 61-(2). Compounds 64~67 (Examples 64~67) were prepared using the compound obtained in Example 61-(1), in the same manner as described in Example 22-(1) followed by the reaction with the corresponding amines, methylamine, piperazine,

N-methyl-piperazine, morpholine in the same manner as described in Example 22-(2).

EXAMPLE 62

5 Compound 62

appearance: yellow oil

IR(neat, cm^{-1}): 3376, 2944, 1635, 1605, 1584, 1539, 1497, 1470, 1437, 1374, 1341, 1263, 1221, 1152, 1122, 1086, 1029, 756

10 High Resolution FAB-MS(m/z , $(\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_5+\text{H})^+$):

Calcd.: 478.2342

Found : 478.2365

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

15 2.42(3H,d,J=4.9Hz), 2.75-2.92(1H,m), 2.82(1H,dd, J=9.7Hz, 13.1Hz), 3.07(1H,dd,J=3.7Hz, 13.1Hz), 3.23-3.33(1H,m), 3.34-3.42(1H,m), 3.69(3H,s), 3.86(3H, s), 3.87(3H,s), 4.08-4.18(1H,m), 4.76-4.84(1H,m), 5.12(1H,d, J=11.6Hz), 5.23(1H,d,J=11.6Hz), 6.47(1H, s), 6.48-6.56(2H,m), 6.68-6.74(1H,m), 7.11(1H,t, J=8.1Hz), 7.33(1H, dd,J=4.9Hz, 7.6Hz), 7.77-7.82(1H, m), 8.58-8.64(1H,m), 8.71-8.77(1H,m)

EXAMPLE 63

20

Compound 63

appearance: pale yellow oil

High Resolution FAB-MS(m/z , $(\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_5+\text{H})^+$):

25 Calcd.: 478.2342

Found : 478.2320

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

30 2.47(3H,d,J=4.6Hz), 2.50-2.70(1H,m), 2.78-2.95(2H, m), 3.08(1H,dd,J=4.1Hz, 12.2Hz), 3.29-3.42(1H,m), 3.49-3.60(1H,m), 3.66(3H,s), 3.78(3H,s), 3.87(3H, s), 3.94-4.10(1H,m), 5.01(1H,dd,J=4.1Hz, 8.7Hz), 5.11(2H,s), 6.48(1H,s), 6.50-6.70(2H,m), 6.66-6.76 (1H,m), 7.10(1H,t,J=7.7Hz), 7.41(2H,d,J=5.4Hz), 8.12-8.30(2H,m)

EXAMPLE 64

Compound 64

35

appearance: pale yellow powder

IR(KBr, cm^{-1}): 2944, 1608, 1545, 1497, 1470, 1260, 1122, 753

High Resolution FAB-MS(m/z , $(\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_5+\text{H})^+$):

Calcd.: 520.2812

40 Found : 520.2804

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

45 2.46(3H,s), 2.58(3H,d,J=4.4Hz), 2.50-2.64(1H,m), 2.73(1H,dd,J=9.5Hz, 13.4Hz), 2.75-2.87(1H,m), 2.98 (1H, dd,J=4.0Hz, 13.4Hz), 3.40-3.51(1H,m), 3.52-3.70 (1H,m), 3.68(3H,s), 3.86(3H,s), 3.92(3H,s), 3.88(1H, d,J=12.1Hz), 4.11(1H,d,J=12.1Hz), 4.94(1H,d, J=11.8Hz), 5.41(1H,d,J=11.8Hz), 5.26-5.40(1H,m), 6.36(1H,d,J=7.7Hz), 6.40 (1H,d,J=2.1Hz), 6.42(1H, s), 6.68(1H,dd,J=2.1Hz, 7.7Hz), 7.07(1H,t,J=7.7Hz), 7.35(1H,d,J=7.6Hz), 7.39(1H,t,J=7.6Hz), 7.58(1H,d, J=7.6Hz), 7.61(1H,s)

EXAMPLE 65

50 Compound 65

appearance: colorless powder

IR(KBr, cm^{-1}): 1635, 1605, 1539, 1497, 1461, 1341, 1263, 1122, 753

High Resolution FAB-MS (m/z , $(\text{C}_{33}\text{H}_{42}\text{N}_4\text{O}_5+\text{H})^+$):

55 Calcd.: 575.3234

Found : 575.3244

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

2.33(3H,d,J=4.6Hz), 2.38-2.50(4H,m), 2.56(1H,td, J=4.0Hz, 16.1Hz), 2.74(1H,dd,J=10.0Hz, 13.3Hz), 2.75-

2.90(1H,m),2.85-2.97(4H,m),3.11(1H,dd, J=2.8Hz,13.3Hz),3.16-3.30(1H,m),3.52(2H,s),3.69 (3H,s),3.87(3H,s),
3.91(3H,s),4.15-4.25(1H,m), 4.63(1H,dd,J=2.8Hz,10.0Hz),5.13(1H,d,J=11.2Hz), 5.29(1H,d,J=11.2Hz),6.44(1H,
s),6.46(1H,d, J=7.7Hz),6.51(1H,d,J=2.4Hz),6.70(1H,dd,J=2.4Hz, 7.7Hz),7.07(1H,t,J=7.7Hz),7.25-7.45(4H,m)

5 EXAMPLE 66

Compound 66

appearance: pale yellow powder

10 IR(KBr, cm⁻¹): 1635,1605,1539,1497,1461,1344,1260, 1122

High Resolution FAB-MS(m/z, (C₃₄H₄₄N₄O₅+H)⁺):

Calcd.: 589.3390

Found : 589.3385

¹H-NMR(300MHz, CDCl₃, δ ppm):

15 2.30(3H,s),2.33(3H,d,J=4.6Hz),2.35-2.60(8H,m), 2.57(1H,td,J=3.6Hz,16.2Hz),2.76(1H,dd,J=10.1Hz, 13.
3Hz),2.79-2.92(1H,m),3.12(1H,dd,J=3.0Hz, 13.3Hz),3.15-3.30(1H,m),3.50(2H,s),3.69(3H,s), 3.87(3H,s),3.91(3H,
s),4.23-4.33(1H,m),4.62(1H, dd,J=3.0Hz,10.1Hz),5.11(1H,d,J=11.1Hz),5.29(1H, d,J=11.1Hz),6.45(1H,s),6.48
(1H,d,J=7.5Hz),6.52 (1H,d,J=2.5Hz),6.69(1H,dd,J=2.5Hz,7.5Hz),7.07 (1H,t,J=7.5Hz),7.31-7.45(4H,m)

20 EXAMPLE 67

Compound 67

appearance: colorless powder

25 IR(KBr, cm⁻¹): 2944,1638,1605,1536,1497,1458,1341, 1266,1119

High Resolution FAB-MS(m/z, (C₃₃H₄₁N₃O₆+H)⁺):

Calcd.: 576.3074

Found : 576.3058

¹H-NMR(300MHz, CDCl₃, δppm):

30 2.33(3H,d,J=4.6Hz),2.40(4H,t,J=4.6Hz),2.57(1H, td,J=3.4Hz,15.9Hz),2.76(1H,dd,J=10.0Hz,13.3Hz), 2.75-
2.90(1H,m),3.12(1H,dd,J=10.0Hz,13.3Hz), 3.15-3.30(1H,m),3.46(1H,d,J=13.4Hz),3.50(1H,d, J=13.4Hz),3.66(4H,
t,J=4.6Hz),3.69(3H,s),3.87(3H, s),3.90(3H,s),4.20-4.32(1H,m),4.62(1H,dd, J=2.8Hz,10.0Hz),5.12(1H,d,J=11.2Hz),
5.29(1H,d, J=11.2Hz),6.45(1H,s),6.48(1H,d,J=7.6Hz),6.53(1H, d,J=2.2Hz),6.70(1H,dd,J=2.2Hz,7.6Hz),7.07(1H,
t, J=7.6Hz),7.30-7.48(4H,m)

35

EXAMPLE 68

Preparation of Compound 68

40 To a solution of compound 30 obtained in Example 30-(2) (25.4 mg, 0.0475 mmole) in dichloromethane
(0.6 ml) were added 4-dimethylaminopyridine (5.8 mg, 0.047 mmole) and acetic anhydride (5.3 μl, 0.056
mmole), and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was con-
centrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography
(Merck, silica gel 60F₂₅₄/chloroform:methanol=10:1) to give the captioned compound (20.4 mg) as a colorless
45 oil.

IR(neat, cm⁻¹): 2944,2820,2765,1755,1671,1614,1515, 1458,1371, 1248,1122,1032,838,785

High Resolution FAB-MS (m/z, (C₃₃H₄₀N₂O₇+H)⁺):

Calcd.: 577.2914

Found : 577.2945

50 ¹H-NMR(300MHz, CDCl₃, δ ppm):

2.03+2.16(3H,s × 2),2.24+2.29(6H,s × 2),2.64-2.96 (2H,m),2.74(1H,dd,J=10.5Hz,13.7Hz),3.02(1H,d,
J=14.4Hz),3.07(1H,dd,J=2.0Hz,13.7Hz),3.20(1H,dt, J=4.5Hz,12.5Hz),3.46+3.55(2H,s × 2),3.74+3.76(3H, s ×
2),3.85+3.88(3H,s × 2),3.86+3.93(3H,s × 2),4.17 (1H,d,J=14.4Hz),4.55+5.90(1H,dd × 2,J=2.0Hz, 10.5Hz,
J=5.5Hz,7.3Hz),4.67-4.77(1H,m),5.03+5.09 (1H,d × 2,J=11.0Hz,J=11.0Hz),5.41(1H,d,J=11.0Hz), 6.39+6.45
55 (1H,s × 2),6.64-6.82(4H,m),7.31-7.50(4H, m)

EXAMPLE 69

Preparation of Compound 69

5 The captioned compound was prepared as a colorless oil (yield: 21.8 mg) using compound 30 obtained in Example 30-(2) (55.4 mg, 0.104 mmole), in the same manner as described in Example 30-(2).

IR(neat, cm^{-1}): 3412, 2944, 2836, 1755, 1645, 1611, 1515, 1457, 1240, 1179, 1122, 1080, 1032, 753

High Resolution FAB-MS (m/z , $(\text{C}_{33}\text{H}_{40}\text{N}_2\text{O}_8+\text{H})^+$): 593

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

10 2.24+2.29(6H, s \times 2), 2.43-2.95(3H, m), 2.74(1H, dd, $J=10.5\text{Hz}$, 13.9Hz), 3.06(1H, dd, $J=2.3\text{Hz}$, 13.9Hz), 3.11-3.29(1H, m), 3.16(1H, d, $J=14.2\text{Hz}$), 3.47(2H, s), 3.76+3.77(3H, s \times 2), 3.86+3.88(3H, s \times 2), 3.93+3.94 (3H, s \times 2), 4.08(1H, d, $J=14.2\text{Hz}$), 4.07-4.35(2H, m), 4.50+5.83(1H, dd \times 2, $J=2.3\text{Hz}$, 10.5Hz , $J=5.7\text{Hz}$, 7.8Hz), 4.60-4.71(1H, m), 5.14+5.16(1H, d \times 2, $J=11.2\text{Hz}$, $J=11.2\text{Hz}$), 5.39+5.40(1H, d \times 2, $J=11.2\text{Hz}$, $J=11.2\text{Hz}$), 6.39+6.46(1H, s \times 2), 6.63-6.71(4H, m), 7.29-7.48(4H, m)

EXAMPLE 70

Preparation of compound 70

20 To a solution of compound 47 obtained in Example 47-(2) (19.5 mg, 0.0329 mmole) in methanol (0.5 ml) was added an aqueous potassium hydroxide solution (1N, 65 μl) under an argon atmosphere, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform: methanol=10:1) to give the captioned compound (14.5 mg) as a colorless oil.

25 IR(neat, cm^{-1}): 2938, 2820, 1644, 1515, 1458, 1434, 1248, 1122, 1089, 1032, 753

High Resolution FAB-MS(m/z , $(\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_6\text{S}+\text{H})^+$):

Calcd.: 551.2579

Found : 551.2584

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δ ppm):

30 2.27+2.30(6H, s \times 2), 2.28-2.57(2H, m), 2.59-2.98(3H, m), 3.01-3.39(3H, m), 3.42-3.63(2H, m), 3.69+3.72(3H, s \times 2), 3.76+3.86(3H, s \times 2), 3.89+3.95(3H, s \times 2), 4.57-4.71(1H, m), 4.71-4.86+5.96-5.97(1H, m \times 2), 4.93-5.11(1H, m), 5.33-5.51(1H, m), 6.39+6.47(1H, s \times 2), 6.56-6.87(4H, m), 7.33-7.58(4H, m)

EXAMPLE 71

Preparation of compound 71

35 The captioned compound was prepared as a yellow oil (yield: 48.3 mg) using intermediate 2 obtained in Referential Example 2 (90.0 mg, 0.252 mmole) and 3-nitrobenzyl chloride (56.1 mg, 0.327 mmole) in the same manner as described in Example 1-(1).

FAB-MS (m/z , $(\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_7+\text{H})^+$): 493

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δppm):

45 2.60-3.00(2H, m), 3.09(1H, dd, $J=2.7\text{Hz}$, 13.7Hz), 3.14-3.28(1H, m), 3.45-3.53(1H, m), 3.69(3H, s), 3.88(3H, s), 3.89(3H, s), 4.43(1H, ddd, $J=2.5\text{Hz}$, 6.3Hz , 12.6Hz), 4.55+5.71-5.77(1H, dd+m, $J=2.7\text{Hz}$, 10.5Hz), 5.19+5.25 (1H, d \times 2, $J=12.0\text{Hz}$, 12.0Hz), 5.39(1H, d, $J=12.0\text{Hz}$), 6.39+6.44(1H, s \times 2), 6.47-6.60(2H, m), 6.69-6.80(1H, m), 7.08+7.12(1H, t \times 2, $J=7.7\text{Hz}$, 7.7Hz), 7.43+8.00 (1H, s \times 2), 7.58+7.60(1H, t \times 2, $J=7.8\text{Hz}$, 7.8Hz), 7.78-7.88(1H, m), 8.19-8.30(1H, m), 8.36-8.42(1H, m)

EXAMPLE 72

Preparation of Compound 72

50 To a solution of Compound 71 obtained in Example 71 (48.0 mg, 0.0975 mmole) in ethanol (2 ml) was added tin(II) chloride (93.2 mg, 0.492 mmole) under nitrogen, and the reaction mixture was stirred at 70°C for 1 hour. To the mixture was added an aqueous sodium hydrogen-carbonate solution, and the mixture was extracted with chloroform. The combined extracts were dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform: methanol=20:1) to give the captioned compound (29.2 mg) as a yellow oil.

IR(neat, cm^{-1}): 3370, 2938, 1668, 1605, 1497, 1458, 1437, 1374, 1344, 1296, 1266, 1236, 1188, 1155, 1122, 1083, 1032, 1005, 963, 861, 753, 699

High Resolution FAB-MS (m/z , $(\text{C}_{27}\text{H}_{30}\text{N}_2\text{O}_5+\text{H})^+$):

Calcd.: 463.2233

Found : 463.2270

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δppm):

2.71(1H, dd, $J=11.0\text{Hz}$, 13.6Hz), 2.62-2.92(2H, m), 3.15(1H, dd, $J=2.4\text{Hz}$, 13.6Hz), 3.10-3.21(1H, m), 3.69+3.73(3H, s \times 2), 3.85+3.88(3H, s \times 2), 3.89+3.93(3H, s \times 2), 4.33-4.42+5.85-5.90(2H, m \times 2), 5.01+5.02(1H, d \times 2, $J=11.0\text{Hz}$, $J=11.0\text{Hz}$), 5.23+5.24(1H, d \times 2, $J=11.0\text{Hz}$, $J=11.0\text{Hz}$), 6.39+6.46(1H, s \times 2), 6.51-6.60(2H, m), 6.62-6.68(1H, m), 6.69-6.80(3H, m), 7.07-7.20(2H, m), 7.22+7.97(1H, s \times 2)

EXAMPLE 73

Preparation of Compound 73

To a solution of compound 24 (20.0 mg, 0.0355 mmole) in acetone (2 ml) was added an aqueous oxone solution (2 ml, 0.0223 mmole), and the reaction mixture was stirred at room temperature for 15 hours. Water was added to the mixture, and the mixture was extracted with chloroform. The combined extracts were dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (Merck, silica gel 60F₂₅₄/chloroform: methanol=20:1) to give the captioned compound (14.3 mg) as a colorless oil.

IR(neat, cm^{-1}): 2938, 2830, 1671, 1605, 1584, 1497, 1458, 1437, 1368, 1344, 1269, 1236, 1188, 1155, 1122, 1083, 1056, 1032, 960, 753, 699

High Resolution FAB-MS(m/z , $(\text{C}_{32}\text{H}_{38}\text{N}_2\text{O}_6\text{S}+\text{H})^+$):

Calcd.: 579.2529

Found : 579.2535

$^1\text{H-NMR}$ (300MHz, CDCl_3 , δppm):

2.56-3.32(13H, m), 3.53(2H, s), 3.67+3.71(3H, s \times 2), 3.86+3.88(3H, s \times 2), 3.93(3H, s), 4.29-4.42+5.72-5.78(2H, m \times 2), 5.12+5.16(1H, d \times 2, $J=11.4\text{Hz}$, $J=11.4\text{Hz}$), 5.28+5.32(1H, d \times 2, $J=11.4\text{Hz}$, $J=11.4\text{Hz}$), 6.40-6.54(3H, m), 6.66-6.73(1H, m), 7.05+7.10(1H, t \times 2, $J=7.9\text{Hz}$, $J=7.9\text{Hz}$), 7.19-7.53(4H, m), 7.35-7.97(1H, s \times 2)

EXAMPLE 74

(1) Preparation of (-) optical isomer of Compound 1

The captioned compound was prepared as a colorless oil using (-)-6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol obtained in Referential Example 11-(1), in the same manner as described in Referential Example 1 and Example 1-(1).

Optical Rotation: $[\alpha]_D^{25} = -83.0^\circ$ (C=0.684, chloroform)

(2) Preparation of (+) optical isomer of compound 1

The captioned compound was prepared as a colorless oil using (+)-6,7-dimethoxy-1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-8-ol obtained in Referential Example 11-(2), in the same manner as described in Referential Example 1 and Example 1-(1).

Optical Rotation: $[\alpha]_D^{25} = +82.1^\circ$ (C=0.702, chloroform)

Compound 75 (Example 75) was prepared using compound 4 obtained in Example 4, in the same manner as described in Example 30.

EXAMPLE 75

Compound 75

appearance: yellow oil

IR(neat, cm^{-1}): 2932, 2854, 2776, 1650, 1611, 1584, 1518, 1500, 1461, 1401, 1374, 1344, 1305, 1248, 1179, 1122, 1083, 1032, 831

High Resolution FAB-MS(m/z , $(\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_6+\text{H})$)

Calcd.: 535.2808

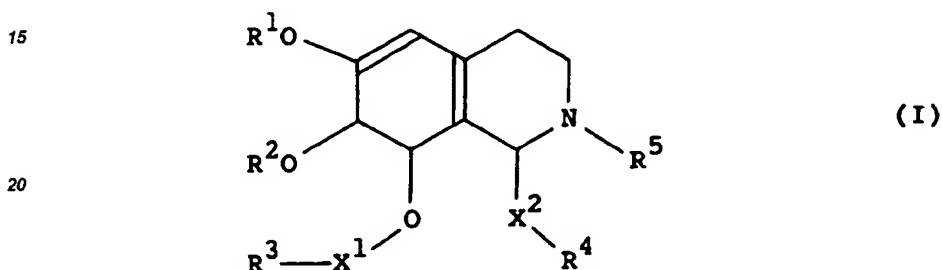
Found : 535.2826

¹H-NMR(300MHz, CDCl₃, δppm):

2.27+2.28(6H,s × 2), 2.37-2.60(1H,m), 2.67(1H,d, J=15.0Hz), 2.73(1H,dd,J=10.5Hz, 13.7Hz), 2.79-2.98
 (1H,m), 3.05(1H,dd,J=2.5Hz, 13.7Hz), 3.18-3.36(1H, m), 3.42(1H,d,J=15.0Hz), 3.49(2H,s), 3.74+3.75(3H,s × 2),
 3.86+3.88(3H,s × 2), 3.93(3H,s), 4.34(1H,dd+m, J=2.5Hz, 10.5Hz), 4.65-4.74(1H,m), 5.06+5.07(1H,d × 2, J=10.9Hz,
 10.9Hz), 5.16+5.38(1H,d × 2, J=10.9Hz, 10.9Hz), 6.40+6.45(1H,s × 2), 6.69+6.70(2H,d × 2, J=8.6Hz, 8.6Hz), 6.77+
 6.79(2H,d × 2, J=8.6Hz, 8.6Hz), 7.32-7.55(4H,m)

10 Claims

1. A compound represented by general formula (I):



25 wherein each of R¹ and R² independently represents a lower alkyl group or both are combined together to form a methylene group;

X¹ represents a divalent alkylene chain having 1 to 5 carbon atoms which may be substituted with a lower alkyl group (one optical methylene group in which alkylene chain may be replaced by one group selected from the group consisting of an oxy group, a thio group, a sulfinyl group, a sulfonyl group or a group shown by formula: -NR⁶, wherein R⁶ represents a hydrogen atom or a lower alkyl group); provided that the said methylene group is not the methylene group adjacent to the oxygen atom at the 8-position of the isoquinoline ring;

X² represents a divalent alkylene chain having 1 to 4 carbon atoms which may be substituted with a lower alkyl group;

35 each of R³ and R⁴ represents independently an aryl group or a heteroaryl group, each of which group may be substituted with 1 to 3 substituents which may be the same or different and are selected from the group consisting of a lower alkyl group, a lower alkoxy group, a methylenedioxy group, a halogen atom, a nitro group, a hydroxy group, a cyano group, a lower alkoxy carbonyl group, a lower alkanoyl group, an amino group, an N-mono-lower alkylamino group, an N,N-di-lower alkylamino group, a carbamoyl group, an N-mono-lower alkylcarbamoyl group, an N,N-di-lower alkylcarbamoyl group, an amino-lower alkyl
 40 group, an N-mono-lower alkylamino-lower alkyl group, an N,N-di-lower alkylamino-lower alkyl group, an N-(hydroxy-lower alkyl)amino-lower alkyl group, an N-lower-alkyl-N-(hydroxy-lower alkyl)amino-lower alkyl group, an N,N-di(hydroxy-lower alkyl)amino-lower alkyl group, an N-(lower alkoxy-lower alkyl)amino-lower alkyl group, an N-lower alkyl-N-(lower alkoxy-lower alkyl)amino-lower alkyl group, an N,N-di(lower alkoxy-lower alkyl)amino-lower alkyl group and a nitrogen-containing saturated heterocyclic lower alkyl group; and

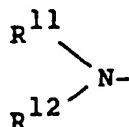
45 R⁵ represents a lower alkoxy carbonyl group a lower alkylsulfonyl group, a group shown by formula:



wherein each of R⁷ and R⁸ independently represents a hydrogen atom or a lower alkyl group which may be substituted with 1 or 2 substituents, which may be the same or different and are selected from the group

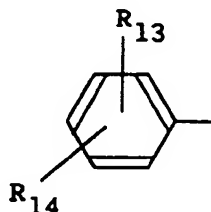
consisting of a hydroxy group and a lower alkoxy group, or both are combined together with the nitrogen atom adjacent thereto to form a saturated nitrogen-containing heterocyclic group; and X represents an oxygen atom or a sulfur atom, or

a lower alkanoyl group which may be substituted with 1 or 2 substituents, which may be the same or different and are selected from the group consisting of a lower alkylsulfinyl group, a group shown by formula: R^9S -wherein R^9 represents a hydrogen atom, a lower alkyl group, a lower alkanoyl group, a carbamoyl group, an N-mono-lower alkylcarbonyl group, an N,N-di-lower alkyl-carbamoyl group or a lower alkoxy carbonyl group; a group shown by formula: $R^{10}O$ - wherein R^{10} represents a hydrogen atom, a lower alkyl group or a lower alkanoyl group which may be substituted with a hydroxy group; and a group shown by formula:

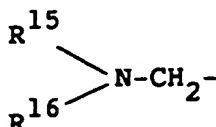


wherein each R^{11} and R^{12} independently represents a hydrogen atom, a lower alkyl group or a lower alkanoyl group, or both are combined together to form a 5- to 7-membered nitrogen-containing saturated heterocyclic ring having 3 to 6 carbon atoms together with the nitrogen atom adjacent thereto, wherein one methylene group not adjacent to the nitrogen atom for forming the ring may be replaced by an oxy group or a thio group and one methylene group adjacent to the nitrogen atom may be replaced by a carbonyl group, and a pharmaceutically acceptable salt thereof.

2. A compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein each of R^1 and R^2 independently represents a lower alkyl group or both are combined together to form a methylene group; R^4 represents a phenyl group wherein 1 to 3 optional hydrogen atoms on the benzene ring may be replaced by 1 to 3 substituents selected from the group consisting of a lower alkoxy group and a methylenedioxy group, or a pyridyl group; X^2 represents CH_2 or CH_2CH_2 ; R^3 represents a group represented by formula:



wherein R^{13} represents a hydrogen atom or a lower alkoxy group; and R^{14} represents an amino group, an N-mono-lower alkylamino group or an N,N-di-lower alkylamino group or represents a group shown by formula:



wherein each of R^{15} and R^{16} independently represents a hydrogen atom or a lower alkyl group wherein a hydrogen atom on the carbon atom not adjacent to the nitrogen atom may be replaced by a hydroxy group or a lower alkoxy group; or both R^{15} and R^{16} are combined together with the nitrogen atom adjacent thereto to form a 5- to 7-membered nitrogen-containing saturated heterocyclic ring having 3 to 6 carbon atoms and in this case, one optional methylene group not adjacent to the nitrogen atom may be replaced by one

group selected from the group consisting of an oxy group, a thio group, a sulfinyl group, a sulfonyl group or a group shown by formula: -NR¹⁷- wherein R¹⁷ represents a hydrogen atom or a lower alkyl group, or a pyridyl group wherein 1 or 2 hydrogen atoms on the pyridine ring may be replaced by 1 or 2 substituents selected from the group consisting of a lower alkoxy group and an N,N-di-lower alkylaminomethyl group.

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3. A compound or a pharmaceutically acceptable salt thereof according to claim 1 for use as a pharmaceutically active ingredient.

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4. A pharmaceutical composition, which comprises a compound or a pharmaceutically acceptable salt thereof according to claim 1, as an active ingredient.

5. A pharmaceutical composition according to claim 4, which is for the treatment of arrhythmia, myocardial infarction or angina pectoris.

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6. A method for the treatment of arrhythmia, myocardial infarction or angina pectoris, which comprises administering to mammal a compound or a pharmaceutically acceptable salt thereof according to claim 1 in a pharmaceutically effective amount.

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7. Use of a compound or a pharmaceutically acceptable salt thereof according to claim 1 for the preparation of a pharmaceutical composition for the treatment of arrhythmia, myocardial infarction or angina pectoris.

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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

EP 92 30 1467

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|---|--|--|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl. 5) |
| X | WO-A-9 002 119 (BANYU PHARMACEUTICAL) * Abstract * --- | 1-4 | C 07 D 217/20 A 61 K 31/47 |
| A | US-A-4 613 606 (R. CLARK et al.) * Claims, columns 6,7 * --- | 1,3-7 | C 07 D 401/06 C 07 D 401/12 |
| A | CHEMICAL ABSTRACTS, vol. 61, no. 2, July 20, 1964, column 1829c-1830d, Columbus, Ohio, US; I. KAZUYOSHI et al.: "Influence of substituents on the direction of ring-closure in the Bischler-Napieralski isoquinoline synthesis" & YAKUGAKU ZASSHI, 84(4), 329-33(1964) * Abstract * ----- | 1,2 | |
| | | | TECHNICAL FIELDS SEARCHED (Int. Cl. 5) |
| | | | C 07 D |
| INCOMPLETE SEARCH | | | |
| <p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims</p> <p>Claims searched completely : Claims searched incompletely : Claims not searched : Reason for the limitation of the search:</p> <p>Remark: Although claim 6 is directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.</p> | | | |
| Place of search THE HAGUE | | Date of completion of the search 14-05-1992 | Examiner HENRY J.C. |
| CATEGORY OF CITED DOCUMENTS | | <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p> | |
| <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> | | | |

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